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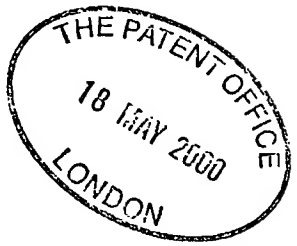
Signed R. Mahoney

Dated 22nd March 2000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Request for grant of a patent

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Cardiff Road
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Your reference — PFIZ\P20959GB

2. Patent application number *(The Patent Office will fill in this part)* — **9912411.7**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

Patents ADP number *(if you know it)* 127001

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — COMPOUNDS USEFUL IN THERAPY

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

ERIC POTTER CLARKSON
PARK VIEW HOUSE
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NOTTINGHAM
NG1 5DD

Patents ADP number *(if you know it)* 1305010

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if.*

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Description	74
Claim(s)	18
Abstract	1
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Priority Documents	0
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	NO
Request for preliminary examination and search *(Patents Form 9/77)*	NO
Request for substantive examination *(Patents Form 10/77)*	NO
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Eric Potter Clarkson Date

ERIC POTTER CLARKSON 27 May 1999

12. Name and daytime telephone number of person to contact in the United Kingdom

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Compounds Useful in Therapy

This invention relates to pharmaceutically useful compounds, in particular compounds that bind to opiate receptors (e.g. mu, kappa and delta opioid receptors).

Compounds that bind to such receptors are likely to be useful in the treatment of diseases mediated by opiate receptors, for example irritable bowel syndrome; constipation; nausea; vomiting; and pruritic dermatoses, such as allergic dermatitis and atopy in animals and humans. Compounds that bind to opiate receptors have also been indicated in the treatment of eating disorders, opiate overdoses, depression, smoking and alcohol addiction, sexual dysfunction, shock, stroke, spinal damage and head trauma.

There is a particular need for an improved treatment of itching. Itching, or pruritus, is a common dermatological symptom that can give rise to considerable distress in both humans and animals. Pruritus is often associated with inflammatory skin diseases which may be caused by hypersensitivity reactions, including reactions to insect bites, such as flea bites, and to environmental allergens, such as house dust mite or pollen; by bacterial and fungal infections of the skin; or by ectoparasite infections.

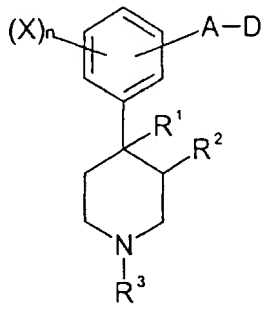
Existing treatments that have been employed in the treatment of pruritus include the use of corticosteroids and antihistamines. However, both of these treatments are known to have undesirable side effects. Other therapies that have been employed include the use of essential fatty acid dietary supplements, though these have the disadvantages of being slow to

act, and of offering only limited efficacy against allergic dermatitis. A variety of emollients such as soft paraffin, glycerine and lanolin are also employed, but with limited success.

Thus, there is a continuing need for alternative and/or improved treatments of pruritus.

Certain 4-arylpiperidine-based compounds are disclosed in *inter alia* European patent applications EP 287339, EP 506468, EP 506478 and *J. Med. Chem.* **1993**, 36, 2833-2850 as opioid antagonists. In addition, International Patent Application WO 95/15327 discloses azabicycloalkane derivatives useful as neuroleptic agents.

According to the invention there is provided compounds of formula I:



I

wherein A represents a single bond, C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH;

D represents H, OH, CN, $N(R^4)(R^5)$, $N(H)R^6$, $C(O)N(R^4)(R^5)$, $C(O)OR^7$, $C(O)R^8$, $C(=NR^{9a})R^8$, or $C(=NOR^{9b})R^8$;

provided that when A represents C_{2-4} alkenylene or C_{2-4} alkynylene, and D represents OH, $N(R^4)(R^5)$ or $N(H)R^6$, then D is not directly attached to an unsaturated carbon atom;

and provided that when A represents a single bond, then D does not represent H, OH, $N(R^4)(R^5)$ or $N(H)R^6$;

R^4 and R^5 independently represent H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, C_{1-4} alkylphenyl, which latter four groups are optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), or R^4 and R^5, together with the N-atom to which they are attached, form a 4- to 7-membered heterocyclic ring, which ring optionally contains one or more additional heteroatoms selected from oxygen, nitrogen and sulfur and which ring is optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, OH, =O, nitro, amino or halo;

R^6 represents $C(O)R^{10a}$, $C(O)OR^{10b}$ or $S(O)_2R^{10c}$;

R^{10a} to R^{10c} independently represent C_{1-4} alkyl, C_{3-8} cycloalkyl, aryl, C_{1-4} alkylphenyl (which four groups are all optionally substituted by or one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms)), or R^{10a} represents H;

R^7 and R^8 independently represent H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or C_{1-4} alkylphenyl, which latter four groups are optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms);

R^{9a} and R^{9b} independently represent C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, C_{1-4} alkylphenyl, which latter four groups are optionally substituted by one

or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), or R^{9b} represents H;

R^1 and R^2 are each independently H or C_{1-4} alkyl;

R^3 represents aryl (optionally substituted by one or more substituents selected from OH, nitro, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms) and $-N(R^{11a})(R^{11b})$), C_{1-10} alkyl, C_{3-10} alkenyl or C_{3-10} alkynyl wherein said alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from OR^{11c}, $S(O)_pR^{11d}$, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^{12a})S(O)_2R^{13}$, Het^1, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or $-W-A^1-N(R^{12b})(R^{12c})$;

p is 0, 1 or 2;

W represents a single bond, C(O) or $S(O)_q$;

A^1 represents a single bond or C_{1-10} alkylene;

provided that when both W and A^1 represent single bonds, then the group $-N(R^{12b})(R^{12c})$ is not directly attached to an unsaturated carbon atom;

q is 0, 1 or 2;

R^{11a} to R^{11d} each independently represent H, C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl, aryl (which latter six groups are optionally substituted by or one or more substituents selected

from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)) or Het^2;

provided that R^{11d} does not represent H when p represents 1 or 2;

R^{12a} to R^{12c} each independently represent H, C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl, aryl (which latter six groups are optionally substituted by or one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), Het^3, or R^{12b} and R^{12c} together represent unbranched C_{2-6} alkylene which alkylene group is optionally interrupted by O, S and/or an $N(R^{14})$ group and is optionally substituted by one or more C_{1-4} alkyl groups;

R^{13} represents C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl or aryl, which four groups are optionally substituted by or one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, OH, nitro, amino or halo;

R^{14} represents H, C_{1-6} alkyl, C_{3-8} cycloalkyl, A^2-(C_{3-8} cycloalkyl) or A^2-aryl;

A^2 represents C_{1-6} alkylene;

Het^1, Het^2 and Het^3 independently represent 3- to 8-membered heterocyclic groups, which groups contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, which groups are optionally fused to a benzene ring, and which groups are optionally substituted in the heterocyclic and/or fused benzene ring part by one or more substituents selected from OH, =O, nitro, amino, halo, CN, aryl, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms);

X is H, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms);

n is 0, 1 or 2;

or pharmaceutically, or veterinarily, acceptable derivatives thereof;

which compounds are referred to together hereinafter as "the compounds of the invention."

In the definitions used herein, alkyl, alkylene, alkoxy, alkoxy carbonyl, alkanoyl, alkanoyloxy, alkenyl, alkynyl and the alkyl parts of alkylphenyl and aryl alkoxy groups may, when there is a sufficient number of carbon atoms, be straight or branched-chain and/or optionally interrupted by one or more oxygen and/or sulfur atom(s). The term halo includes fluoro, chloro, bromo or iodo. The term "aryl" includes optionally substituted phenyl, naphthyl and the like, and "aryloxy" includes optionally substituted phenoxy and naphthyloxy and the like. Unless otherwise specified, aryl and aryloxy groups are optionally substituted by one or more (e.g. one to three) substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy C_{1-4} alkoxy carbonyl and C_{1-5} alkanoyl (which latter four groups are optionally substituted by one or more halo atoms).

The heterocyclic rings that Het^1, Het^2 and Het^3 represent and that $N(R^4)(R^5)$ may represent, may be fully saturated, partially unsaturated and/or wholly or partially aromatic in character.

For the avoidance of doubt, when heterocyclic groups (i.e. Het^1, Het^2, Het^3 and some definitions of $N(R^4)(R^5)$) are at least part-saturated, possible points of substitution include the atom (e.g. the carbon atom) at the point of attachment of the heterocyclic group to the rest of the molecule. Het (Het^1, Het^2 and Het^3) groups may also be attached to the rest of the molecule *via* a heteroatom.

The piperidine moiety in compounds of formula I may be in N-oxidised form. Sulfur atoms that may interrupt (e.g. alkyl) substituents in compounds of formula I may be present in oxidised form (e.g. as sulfoxides or sulfones). All heterocyclic groups (i.e. Het^1, Het^2, Het^3 and some definitions of $N(R^4)(R^5)$) may also be in N- or S-oxidized forms.

The term "pharmaceutically, or veterinarily, acceptable derivatives" includes non-toxic salts. Salts which may be mentioned include: acid addition salts, for example, salts formed with sulfuric, hydrochloric, hydrobromic, phosphoric, hydroiodic, sulfamic, organo-sulfonic, citric, carboxylic (e.g. acetic, benzoic, etc.), maleic, malic, succinic, tartaric, cinnamic, ascorbic and related acids; base addition salts; salts formed with bases, for example, the sodium, potassium and C_{1-4} alkyl ammonium salts.

The compounds of the invention may also be in the form of quaternary ammonium salts, e.g. at the piperdine moiety, which salts may be formed by reaction with a variety of alkylating agents, such as an alkyl halide or an ester of sulfuric, or an aromatic sulfonic, acid.

The compounds of the invention may exhibit tautomerism. All tautomeric forms of the compounds of formula I are included within the scope of the invention.

The compounds of the invention contain one or more asymmetric centres and thus they can exist as enantiomers and diastereomers. Diastereoisomers may be separated using conventional techniques e.g. by fractional crystallisation or chromatography. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional techniques e.g. fractional crystallisation or HPLC. The desired optical isomers may be prepared by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation. Alternatively, the desired optical isomers may be prepared by resolution, either by HPLC of the racemate using a suitable chiral support or, where appropriate, by fractional crystallisation of the diastereoisomeric salts formed by reaction of the racemate with a suitable optically active acid or base. The invention includes the use of both the separated individual isomers as well as mixtures of isomers.

Also included within the scope of the invention are radiolabelled derivatives of compounds of formula I which are suitable for biological studies.

Preferred compounds of the invention include those wherein:

The group A-D is attached in the *meta-* position relative to the piperidine ring;

R^1 represents C_{1-2} alkyl;

R^2 represents H or C_{1-2} alkyl;

R^3 represents saturated C_{1-10} (e.g. C_{1-8}) alkyl, optionally substituted by one or more substituents selected from OR^{11c}, CN, halo, C_{2-4} alkanoyl, C_{1-4} alkoxy carbonyl, $N(R^{12a})SO_2R^{13}$, Het^1, aryl (which latter group is optionally substituted by one or more substituents selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-5} alkanoyl, halo, nitro, amino, CN and $CONH_2$), or $-W-A^1-N(R^{12b})(R^{12c})$;

R^{11c} represents H, C_{1-6} alkyl or aryl (which latter groups is optionally substituted by one or more substituents selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-5} alkanoyl, halo, nitro, amino, CN and $CONH_2$);

R^{12a} to R^{12c} independently represent H, C_{1-4} alkyl, C_{1-2} alkylphenyl or aryl (which latter three groups are optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl or C_{1-4} alkoxy);

R^{13} represents C_{1-4} alkyl, C_{1-2} alkylphenyl or aryl (which three groups are all optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl or C_{1-4} alkoxy);

W represents C(O);

A^1 represents a single bond.

More preferred compounds of the invention include those wherein:

A represents a single bond, C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more OH and/or methyl groups;

D represents H, OH, CN, $N(H)R^4$, $N(H)C(O)R^{10a}$, $N(H)C(O)OR^{10b}$, $N(H)S(O)_2R^{10c}$, $C(O)N(R^4)(R^5)$, $C(O)OR^7$, $C(O)R^8$ or $C(=NOH)R^8$;

R^4 and R^5 independently represent H, C_{1-4} alkyl or C_{1-3} alkylphenyl (which latter two groups are both optionally substituted by C_{1-4} alkoxy);

R^7 and R^8 independently represent H or C_{1-4} alkyl;

R^{10a} to R^{10c} independently represent C_{1-4} alkyl (optionally substituted by one or more halo atoms);

R^1 represents methyl;

R^2 represents H or methyl;

R^3 represents saturated C_{1-7} alkyl, optionally substituted by one or more substituents selected from CN, OR^{11c} or phenyl;

R^{11c} represents C_{1-6} alkyl or phenyl;

X represents halo, particularly fluoro;

n represents 1 or, preferably, 0.

Particularly preferred compounds of the invention include those wherein:

A represents a single bond, $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, -CH(OH)-, $-(CH_2)_2-$, -CH=CH-, or -C≡C-;

D represents H, OH, CN, NH_2, $N(H)CH_3$, CHO, CH(=NOH), $C(O)CH_3$, CO_2CH_3, CO_2H, $C(O)NH_2$, $C(O)N(H)CH_3$, C(O)N(H)Et, C(O)N(H)(2-MeOEt), C(O)N(H)*n*-Pr, C(O)N(H)*i*-Pr, C(O)N(H)*n*-Bu, C(O)N(H)*i*-Bu, C(O)N(H)*t*-Bu, $C(O)N(H)CH_2Ph$, $C(O)N(CH_3)_2$, $C(O)N(Et)_2$, $N(H)C(O)CH_3$, $N(H)C(O)OCH_3$, $N(H)S(O)_2CH_3$ or $N(H)S(O)_2CF_3$;

R^1 and R^2 represent methyl groups in the mutually *trans* configuration;

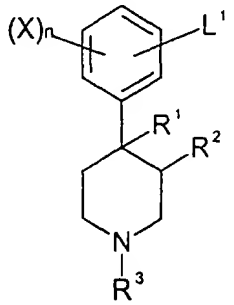
R^3 represents benzyl, 5-cyanopentyl, *n*-hexyl, 5-methylhexyl, 2-phenoxyethyl or 3-phenylpropyl.

Preferred compounds of the invention include the compounds of the Examples described hereinafter.

According to a further aspect of the invention there is provided processes for the preparation of compounds of the invention, as illustrated below.

The following processes are illustrative of the general synthetic procedures which may be adopted in order to obtain the compounds of the invention.

1. Compounds of formula I in which A represents C_{2-4} alkynylene (in which group the carbon-carbon triple bond is α,β to the benzene ring), which alkynylene group is optionally substituted at the 3- and/or the 4-C (relative to the benzene ring) by one or more substituents defined hereinbefore in respect of A, and/or one of the groups defined hereinbefore in respect of D, or (when D is not attached at the 3- or 4-C) which alkynylene group is substituted at the 2-C (relative to the benzene ring) by CN, $C(O)N(R^4)(R^5)$, $C(O)OR^7$, $C(O)R^8$, $C(=NR^{9a})R^8$, or $C(=NOR^{9b})R^8$, may be prepared by reaction of a corresponding compound of formula II,



II

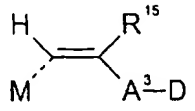
wherein L^1 is a suitable leaving group such as halogen, preferably bromine or iodine, or a sulfonate such as trifluoromethanesulfonate, and R^1, R^2, R^3, X and n are as hereinbefore defined, with a compound of formula III,

III

wherein M represents (as appropriate) H, a tin-containing moiety (e.g. tributylstannyl), a boron derivative (e.g. a boronic acid), a zinc halide, a magnesium halide or an alkali metal (which latter three groups may be formed *in situ* from the corresponding halide), A^3 represents a single bond or C_{1-2} alkylene (optionally substituted by one or more substituents

selected from C_{1-4} alkyl, C_{1-4} alkoxy, OH or halo), and D is as hereinbefore defined, provided that when A^3 represents a single bond, then D does not represent H, OH, $N(R^4)(R^5)$ or $N(H)R^6$, wherein R^4, R^5 and R^6 are as hereinbefore defined, for example at between room and reflux temperature in the presence of a suitable catalyst system (e.g. bis(triphenylphosphine)palladium(II) chloride combined with copper(I) iodide) and an appropriate organic base (e.g. triethylamine).

2. Compounds of formula I in which A represents C_{2-4} alkenylene (in which group the carbon-carbon double bond is α,β to the benzene ring), which alkenylene group is optionally substituted at the 2-C (relative to the benzene ring) by C_{1-4} alkyl, and also optionally substituted at the 3- and/or 4-C (relative to the benzene ring) by one or more of the substituents defined hereinbefore in respect of A and/or one of the groups defined hereinbefore in respect of D, or which alkenylene group is substituted at the 2-C (relative to the benzene ring) by CN, $C(O)N(R^4)(R^5)$, $C(O)OR^7$, $C(O)R^8$, $C(=NR^{9a})R^8$, or $C(=NOR^{9b})R^8$, may be prepared by reaction of a corresponding compound of formula II, as hereinbefore defined, with a compound of formula IV,

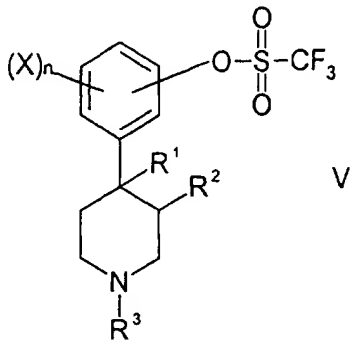


IV

wherein the dashed bond represent optional *cis*- or *trans*- geometry, R^{15} represents H or C_{1-4} alkyl, and A^3, D and M are as hereinbefore defined, for example at between room temperature and reflux temperature in the presence of a reaction-inert solvent (e.g. 1,4-dioxan or THF), an appropriate catalyst (e.g. tetrakis(triphenylphosphine)palladium(0) or bis(triphenylphosphine)palladium(II) acetate) and either (as appropriate) a

suitable source of halide ion (e.g. lithium chloride) or a suitable base (e.g. triethylamine).

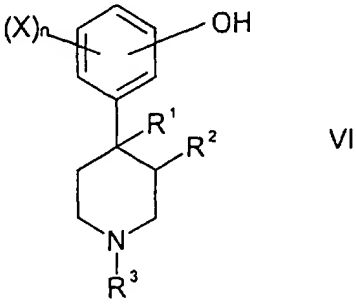
3. Compounds of formula I in which A represents a single bond and D represents CN may be prepared by reaction of a compound of formula V,



V

wherein R^1, R^2, R^3, X and n are as hereinbefore defined with an alkali metal cyanide (e.g. potassium cyanide), for example at raised temperature in the presence of a reaction-inert solvent (e.g. N-methylpyrrolidine) and a suitable catalyst (e.g. palladium(II) acetate combined with 1,1'-bis(diphenylphosphino)ferrocene).

Compounds of formula V may be prepared by reaction of a corresponding compound of formula VI,

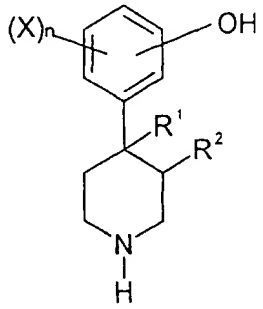


VI

wherein R^1, R^2, R^3, X and n are as hereinbefore defined, with an appropriate triflating agent (e.g. *N*-phenyltrifluoromethanesulfonimide), for example at between 0°C and room temperature in the presence of a

reaction-inert organic solvent (e.g. dichloromethane) and a suitable base (e.g. triethylamine).

Compounds of formula VI may be prepared by reaction of a corresponding compound of formula VII,



VII

in which R^1, R^2, X and n are as hereinbefore defined, with a compound of formula VIII,

R^3-L^1 VIII

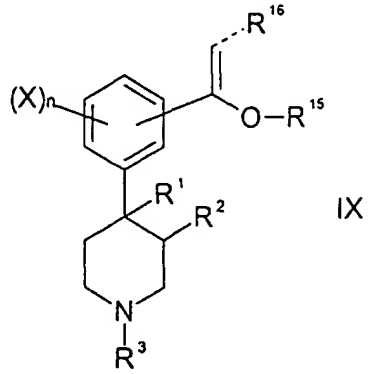
wherein R^3 and L^1 are as hereinbefore defined, under conditions that are known to those skilled in the art, which include, for example, alkylation at between room temperature and reflux temperature in the presence of a reaction-inert organic solvent (e.g. *N,N*-dimethylformamide) and a suitable base (e.g. $NaHCO_3$), and arylation at between room temperature and reflux temperature in the presence of a suitable catalyst system (e.g. tris(dibenzylideneacetone)palladium(0) combined with tri-*o*-tolyl-phosphine), an appropriate strong base (e.g. sodium *tert*-butoxide) and a reaction-inert solvent (e.g. toluene).

4. Compounds of formula I in which A represents C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents NH_2

(which is attached to a CH_2 group) may be prepared by reduction of a corresponding compound of formula I in which A represents (as appropriate) a single bond, C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents CN, for example at between room and reflux temperature in the presence of a suitable reducing agent (e.g. lithium aluminium hydride) and an appropriate solvent (e.g. THF).

5. Compounds of formula I in which D represents $C(O)NH_2$ may be prepared by controlled hydrolysis of a corresponding compound of formula I in which D represents CN, for example by reaction with polyphosphoric acid at between 50 and 150°C.

6. Compounds of formula I in which A represents a single bond and D represents C(O)-(C_{1-6} alkyl) or C(O)-(C_{1-4} alkylphenyl), which alkyl and alkylphenyl groups are both optionally substituted by one or more of the substituents defined hereinbefore in respect of R^8, may be prepared by hydrolysis of a corresponding compound of formula IX,

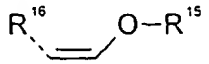


IX

wherein R^{15} represents C_{1-6} alkyl, R^{16} represents H, C_{1-5} alkyl, phenyl or C_{1-3} alkylphenyl which latter three groups are all optionally substituted by

one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), the dashed bond indicates optional *cis*- or *trans*- geometry, and R^1, R^2, R^3, X and n are as hereinbefore defined, for example under conditions known to those skilled in the art (e.g. by reaction at between room and reflux temperature with an aqueous solution of a mineral acid).

Compounds of formula IX may be prepared by reaction of a compound of formula II, as hereinbefore defined, with a compound of formula X,



X

wherein the dashed bond indicates optional *cis*- or *trans*- geometry, and R^{15} and R^{16} are as hereinbefore defined, for example at between room temperature and reflux temperature in the presence of an appropriate catalyst (e.g. palladium(II) acetate combined with 1,1'-bis(diphenylphosphino)ferrocene), an organic base (e.g. triethylamine) and an appropriate solvent (e.g. *N,N*-dimethylformamide).

7. Compounds of formula I in which D represents $C(O)R^8$, wherein R^8 is as hereinbefore defined provided that it does not represent H, may be prepared by reaction of a corresponding compound of formula I in which D represents CN with an organometallic compound capable of delivering an R^{8a}-containing anion (e.g. an appropriate organolithium or Grignard reagent), wherein R^{8a} is defined as for R^8 above provided that it does not represent H, for example at between -80 and 10°C in the presence of a reaction-inert organic solvent (e.g. tetrahydrofuran).

8. Compounds of formula I in which A represents a single bond and D represents $C(O)OR^7$, wherein R^7 is as hereinbefore defined provided that it does not represent H, may be prepared by reaction of a corresponding compound of formula V, as hereinbefore defined, with carbon monoxide and an alcohol of formula $R^{7a}OH$, wherein R^{7a} is defined as for R^7 above provided that it does not represent H, for example in the presence of a suitable transition-metal catalyst system (e.g. palladium(II) acetate combined with 1,1'-bis(diphenylphosphino)ferrocene) and a reaction-inert solvent (e.g. DMF).

9. Compounds of formula I in which A represents C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents OH (which is attached to a CH_2 group) may be prepared by reduction of a corresponding compound of formula I in which A represents (as appropriate) a single bond, C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents $C(O)OR^{7a}$, wherein R^{7a} is as hereinbefore defined, for example at between 0°C and reflux temperature in the presence of a suitable reducing agent (e.g. lithium aluminium hydride) and an appropriate solvent (e.g. THF).

10. Compounds of formula I in which A represents C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are *gem*-disubstituted with two C_{1-4} alkyl groups (α to D) and are optionally substituted by one or more further substituents

selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents OH, may be prepared by reaction of a corresponding compound of formula I in which A represents (as appropriate) a single bond, C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents $C(O)OR^{7a}$, wherein R^{7a} is as hereinbefore defined, with a suitable C_{1-4} alkyl-delivering organometallic compound (e.g. an alkylmagnesium halide), for example at between -10°C and reflux temperature in the presence of a suitable solvent (e.g. THF).

11. Compounds of formula I in which D represents $C(O)N(R^4)(R^5)$, wherein R^4 and R^5 are as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula I in which D represents $C(O)OR^{7a}$, and R^{7a} is as hereinbefore defined, with a compound of formula XI,

$$HN(R^4)(R^5) \qquad XI$$

or an acid (e.g. HCl) addition salt thereof, wherein R^4 and R^5 are as hereinbefore defined, for example at a temperature of between -10 and +150°C and a pressure of between 1 and 10 atmospheres, optionally in the presence (as appropriate) of a Lewis-acidic catalyst (e.g. trimethylaluminium) and a reaction-inert solvent (e.g. toluene).

12. Compounds of formula I in which D represents $C(O)N(R^4)(R^5)$, wherein R^4 and R^5 are as hereinbefore defined, may alternatively be prepared by reaction of a corresponding compound of formula I in which D represents C(O)OH with a compound of formula XI, as hereinbefore defined, under coupling conditions known to those skilled in the art.

13. Compounds of formula I in which D represents C(O)OH may be prepared by hydrolysis of a corresponding compound of formula I in which D represents $C(O)OR^{7a}$, wherein R^{7a} is as hereinbefore defined, under conditions that are known to those skilled in the art.

14. Compounds of formula I in which D represents $N(H)R^6$, wherein R^6 is as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula I in which D represents NH_2 with a compound of formula XII,

$$R^6\text{-}L^1 \qquad \text{XII}$$

wherein R^6 and L^1 are as hereinbefore defined, for example under conditions that are known to those skilled in the art, which include reaction at between -10°C and reflux temperature in the presence of a suitable base (e.g. triethylamine or pyridine) and, optionally, a reaction-inert solvent (e.g. THF or dichloromethane).

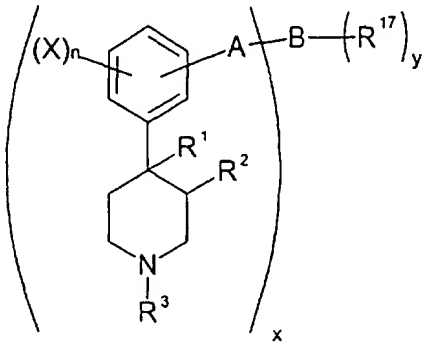
15. Compounds of formula I in which A represents $C_{1\text{-}4}$ alkyl and D represents $N(R^4)(R^5)$ or $N(H)C(O)R^{10a}$ attached at the 1-, 2- or 3-C (relative to the benzene ring), wherein R^4, R^5 and R^{10a} are as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula I in which A represents $C_{1\text{-}4}$ alkenylene unsaturated α,β-, β,γ- or γ,δ- (respectively) relative to the benzene ring and D represents H, with a compound of formula XI, as hereinbefore defined, or a compound of formula XIII,

$$NC\text{-}R^{10a} \qquad \text{XIII}$$

wherein R^{10a} is as hereinbefore defined, for example at between -10°C and room temperature in the presence of a suitable mercury(II) salt (e.g.

mercury(II) acetate, trifluoroacetate, nitrate, or perchlorate), optionally in the presence of a reaction-inert solvent (e.g. THF), and followed by *in situ* reduction of the mercury adduct by the addition of a suitable hydride-delivering agent (e.g. sodium borohydride), optionally in the presence of water.

16. Compounds of formula I in which A represents C_{2-4} alkylene optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents OH may be prepared by oxidation of a corresponding borane adduct of formula XIV,



XIV

wherein x is 1, 2 or 3, y is (as appropriate) (3-x) or 1, R^{17} is (as appropriate) H, halo, an alkyl, or a cycloalkyl group providing one or two bonds to boron (e.g. disiamyl or thexyl), A represents (as appropriate) C_{2-4} alkylene optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and R^1, R^2, R^3, X and n are as hereinbefore defined, for example by reaction with a tertiary amine *N*-oxide (e.g. trimethylamine *N*-oxide) at between room and reflux temperature in the presence of a reaction-inert solvent (e.g. THF or a THF/diglyme mixture).

The skilled person will appreciate that, in compounds of formula XIV, bonds between boron atoms and piperidine N-atoms may be present.

Compounds of formula XIV may be prepared by reaction of a corresponding compound of formula I in which A represents (as appropriate) C_{2-4} alkenylene optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents H with borane or a suitable derivative thereof (e.g. thexyl-borane, disiamylborane or 9-borabicyclo[3.3.1]nonane), for example at between -10°C and room temperature in the presence of a suitable solvent (e.g. THF or a THF/diglyme mixture).

17. Compounds of formula I in which A represents a C_{2-4} alkylene group substituted (α to D) with an OH group and D represents OH may be prepared by reaction of a corresponding compound of formula I in which A represents a C_{2-4} alkenylene group and D represents H with a suitable dihydroxylating reagent (e.g. sub-stoichiometric OsO_4 combined with 4-methylmorpholine *N*-oxide), for example at between 0°C and reflux temperature in the presence of a reaction-inert solvent (e.g. a water/acetone mixture).

18. Compounds of formula I in which A represents a single bond or a C_{1-2} alkylene group (as appropriate) and D represents C(O)H may be prepared by reaction of a corresponding of formula I in which A represents a C_{2-4} alkylene group substituted (α to D) with an OH group and D represents OH with a reagent that effects 1,2-diol oxidative cleavage (e.g. sodium periodate).

19. Compounds of formula I in which D represents $C(=NR^{9a})R^8$ or $C(=NOR^{9b})R^8$, wherein R^8, R^{9a} and R^{9b} are as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula I in which D represents $C(O)R^8$ with a compound of formula XV,

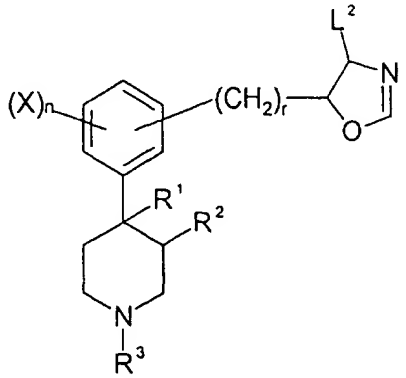
$$H_2N\text{-}R^{9a} \qquad \text{XV}$$

or a compound of formula XVI,

$$H_2N\text{-}OR^{9b} \qquad \text{XVI}$$

wherein R^{9a} and R^{9b} are as hereinbefore defined, for example under conditions that are known to those skilled in the are, which include reaction at between room and reflux temperature in the presence of a suitable solvent (e.g. a lower alkyl alcohol such as methanol or ethanol).

20. Compounds of formula I in which A represents C_{1-4} alkylene substituted (α to D) with an OH group and D represents $N(H)CH_3$ (at the alkylene chain terminus) may be prepared by reduction of a corresponding compound of formula XVII,



XVII

wherein r is 0, 1 or 2, L^2 represents H or a group capable, when attached to a C_2 alkylene unit, of undergoing 1,2-elimination (relative to the L^2 group, e.g. an alkyl or aryl sulfoxide or sulfone), and R^1, R^2, R^3, X and n are as hereinbefore defined, for example, at between -10°C and reflux

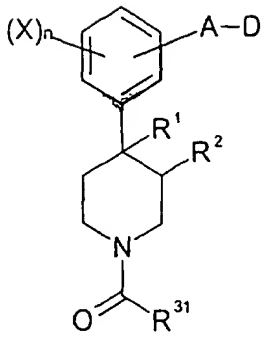
temperature in the presence of a suitable reducing agent (e.g. lithium aluminium hydride) and a reaction-inert solvent (e.g. THF).

Compounds of formula XVII may be prepared by reaction of a corresponding compound of formula I in which A represents a single bond or C_{1-2} alkylene and D represents C(O)H with a compound of formula XVIII,

$$CN\text{-}CH_2\text{-}L^2 \qquad \text{XVIII}$$

wherein L^2 is as hereinbefore defined, for example at between 0°C and reflux temperature in the presence of a suitable solvent (e.g. ethanol) and a catalytic quantity of a cyanide salt (e.g. sodium cyanide).

21. Compounds of formula I wherein R^3 represents C_1 alkyl optionally substituted by C_{3-8} cycloalkyl, Het^1, aryl, adamantyl, (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or R^3 represents C_{2-10} alkyl, C_{3-10} alkenyl or C_{3-10} alkynyl (which three groups are all optionally substituted by one or more of the relevant substituents identified hereinbefore in respect to R^3), which alkyl, alkenyl or alkynyl groups are attached to the piperidine nitrogen atom *via* a CH_2 group, wherein Het^1 is as hereinbefore defined, may be prepared by reduction of a corresponding compound of formula XIX,

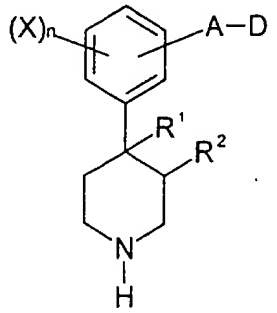


XIX

wherein R^{31} represents H, C_{3-8} cycloalkyl, Het^1, aryl, adamantyl, (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), C_{1-9} alkyl, C_{2-9} alkenyl or C_{2-9} alkynyl, which alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from OR^{11c}, $S(O)_pR^{11d}$, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^{12a})S(O)_2R^{13}$, Het^1, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or -W-A^1-$N(R^{12b})(R^{12c})$, and R^1, R^2, R^{11c}, R^{11d}, R^{12a} to R^{12c}, R^{13}, Het^1, n, p, W, X, A^1, A and D are as hereinbefore defined, using a suitable reducing agent (e.g. lithium aluminium hydride or a borane derivative), for example as described hereinbefore.

The skilled person will appreciate that this reduction may take place simultaneously with other reduction steps described herein (see, for example, processes 4, 9 and 16).

Compounds of formula XIX may be prepared by reaction of a corresponding compound of formula XX,



XX

wherein R^1, R^2, A, D, X and n are as hereinbefore defined with a compound of formula XXI,

$R^{31}CO_2H$ XXI

or a suitable (e.g. carboxylic acid) derivative thereof (e.g. an acid halide or anhydride), wherein R^{31} is as hereinbefore defined, using coupling conditions known to those skilled in the art.

Compounds of formulae XIX and XX may be prepared from appropriate precursors by analogy with methods disclosed hereinbefore that describe the preparation of compounds of formula I.

22. Compounds of formula I may be prepared by reaction of a corresponding compound of formula XX, as hereinbefore defined, with a compound of formula VIII, as hereinbefore defined, under conditions that are well known to those skilled in the art, for example as described hereinbefore in respect of the production of compounds of formula VI.

23. Compounds of formula I wherein R^3 represents C_1 alkyl, which, in place of being optionally substituted by the substituents as defined hereinbefore, is instead optionally substituted by R^{31}, wherein R^{31} is as

hereinbefore defined, may be prepared by reaction of a corresponding compound of formula XX, as hereinbefore defined, with a compound of formula XXII,

$R^{31}CHO$ XXII

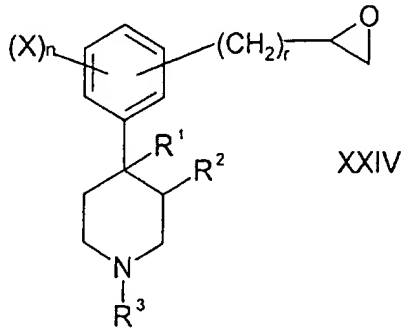
wherein R^{31} is as hereinbefore defined, for example in the presence of a suitable reducing agent (e.g. sodium borohydride, sodium cyano-borohydride or sodium triacetoxyborohydride) and an appropriate solvent (e.g. methanol).

24. Compounds of formula I wherein R^3 is a C_{1-10} alkyl, C_{4-10} alkenyl or C_{4-10} alkynyl group that is fully saturated from 1- to 3-C (relative to the piperidine N-atom), and which R^3 group is substituted at 2-C (relative to the piperidine N-atom) by $S(O)R^{11d}$, $S(O)_2R^{11d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, $-C(O)-A^1-N(R^{12b})(R^{12c})$, $-S(O)-A^1-N(R^{12b})(R^{12c})$, or $-S(O)_2-A^1-N(R^{12b})(R^{12c})$, wherein R^{11d}, R^{12b}, R^{12c} and A^1 are as hereinbefore defined, may be prepared by reaction of a corresponding compound of formula XX, as hereinbefore defined, with a compound of formula XXIII,

R^{3a}-Z XXIII

wherein R^{3a} represents R^3 as hereinbefore defined except that it does not represent aryl, and that the R^{3a} chain contains an additional carbon-carbon double bond α,β to the Z-substituent, and Z represents $S(O)R^{11d}$, $S(O)_2R^{11d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, $-C(O)-A^1-N(R^{12b})(R^{12c})$, $-S(O)-A^1-N(R^{12b})(R^{12c})$, or $-S(O)_2-A^1-N(R^{12b})(R^{12c})$, wherein R^{11d}, R^{12b}, R^{12c} and A^1 are as hereinbefore defined, for example at between room and reflux temperature in the presence of a reaction-inert solvent (e.g. THF).

25. Compounds of formula I in which A represents C_{2-4} alkylene substituted (α to D) with an OH group and D represents $N(R^4)(R^5)$ (at the alkylene chain terminus), and R^4 and R^5 are as hereinbefore defined, may be prepared by reaction of a compound of formula XXIV,



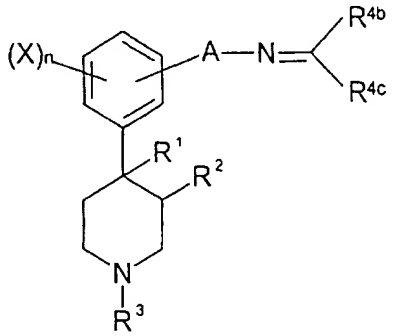
XXIV

wherein R^1, R^2, R^3, X, n and r are as hereinbefore defined, with a compound of formula XI, as hereinbefore defined, for example at between room and reflux temperature in the presence of a suitable base (e.g. potassium carbonate) and an appropriate solvent (e.g. *N,N*-dimethylformamide).

Compounds of formula XXIV may be prepared by dehydration of a corresponding compound of formula I in which A represents a C_{2-4} alkylene substituted (α to D) with an OH group and D represents OH (at the alkylene chain terminus) under conditions well known to those skilled in the art (e.g. by heating in concentrated sulfuric acid).

Compounds of formula XXIV may alternatively be prepared by epoxidation of a corresponding compound of formula I in which A represents a terminal C_{2-4} alkenylene group and D represents H under conditions well known to those skilled in the art (e.g. by reaction with *meta*-chloroperbenzoic acid).

26. Compounds of formula I in which D represents $N(H)R^4$, wherein R^4 is as hereinbefore defined provided that it does not represent aryl, may be prepared by reduction of a corresponding compound of formula XXV,



XXV

wherein R^{4b} and R^{4c}, together with the carbonyl group to which they are attached, form a C_{1-6} alkanal, C_{3-6} alkanone, C_{3-8} cycloalkanone, phenyl(C_{1-4})alkanal or phenyl(C_{2-4})alkanone group, which five groups are optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), and R^1, R^2, R^3, A, X and n are as hereinbefore defined (provided that the $-N=C(R^{4b})(R^{4c})$ group is not directly attached to an unsaturated carbon atom), for example at between room and reflux temperature in the presence of a mild reducing agent (e.g. sodium borohydride) and a suitable solvent (e.g. a lower alkyl alcohol such as methanol or ethanol).

Compounds of formula XXV may be prepared by reaction of a corresponding compound of formula I in which D represents NH_2 with a compound of formula XXVI,

$$R^{4b}C(O)R^{4c} \qquad \text{XXVI}$$

wherein R^{4b} and R^{4c} are as hereinbefore defined, for example at between room and reflux temperature in the presence of a reaction-inert solvent

(e.g. a lower alkyl alcohol such as methanol or ethanol) and optionally in the presence of a Lewis-acidic catalyst.

27. Compounds of formula I in which A represents C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents $N(R^4)(R^5)$ (attached to a CH_2 group), wherein R^4 and R^5 are as hereinbefore defined, may be prepared by reduction of a corresponding compound of formula I in which A represents (as appropriate) a single bond, C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents $C(O)N(R^4)(R^5)$, for example in the presence of a suitable reducing agent (e.g. lithium aluminium hydride or a borane derivative) and a reaction-inert solvent (e.g. THF).

Compounds of formulae II, III, VIII, X, $R^{7a}OH$, XI, XII, XIII, XV, XVI, XVIII, XXI, XXII, XXIII, XXVI, and derivatives thereof, when not commercially available or not subsequently described, may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions.

Substituents on alkyl, heterocyclic and aryl groups in the above-mentioned compounds may also be introduced, removed and interconverted, using techniques which are well known to those skilled in the art. For example,

nitro may be reduced to amino, OH may be alkylated to give alkoxy, alkoxy may be hydrolysed to OH, alkenes may be hydrogenated to alkanes, halo may be hydrogenated to H, etc.

In some cases it is possible to introduce further substituents into the compounds of formula I directly. For example, chlorination of the phenyl group of compounds of formula I, may be performed by reaction with a solution of chlorine in acetic acid.

The skilled person will also appreciate that other various standard substituent or functional group interconversions and transformations within certain compounds of formula I will provide other compounds of formula I.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

It will be appreciated by those skilled in the art that, in the course of carrying out the processes described above, the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups which it is desirable to protect include oxo, OH, amino and carboxylic acid. Suitable protective groups for oxo include acetals, ketals (e.g. ethylene ketals) and dithianes. Suitable protective groups for OH include trialkylsilyl and diarylalkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl) and tetrahydropyranyl. Suitable protective groups for amino include *tert*-butyloxycarbonyl, 9-fluorenylmethoxycarbonyl or benzyloxycarbonyl.

Suitable protective groups for carboxylic acid include C_{1-6} alkyl or benzyl esters. Suitable protective groups for terminal alkynes include trialkylsilyl and diarylalkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl).

The protection and deprotection of functional groups may take place before or after any of the reaction steps described hereinbefore.

Protective groups may be removed in accordance with techniques which are well known to those skilled in the art.

The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by JWF McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 2nd edition, TW Greene & PGM Wutz, Wiley-Interscience (1991).

Persons skilled in the art will also appreciate that, in order to obtain compounds of formula I in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This will depend *inter alia* on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates and the protecting group strategy (if any) to be adopted. Clearly, the type of chemistry involved will influence the choice of reagent that is used in the said synthetic steps, the need, and

type, of protecting groups that are employed, and the sequence for accomplishing the synthesis. The procedures may be adapted as appropriate to the reactants, reagents and other reaction parameters in a manner that will be evident to the skilled person by reference to standard textbooks and to the examples provided hereinafter.

It will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula I, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". Further, certain compounds of formula I may act as prodrugs of other compounds of formula I.

It will be further appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties", for example as described in 'Design of Prodrugs' by H. Bundgaard, Elsevier, **1985** (the disclosure in which document is hereby incorporated by reference), may be placed on appropriate functionalities, when such functionalities are present within compounds of formula I.

All protected derivatives, and prodrugs, of compounds of formula I are included within the scope of the invention.

Pharmaceutically acceptable acid addition salts of the compounds of formula I which contain a basic centre may be prepared in a conventional manner. For example, a solution of the free base may be treated with the

appropriate acid, either neat or in a suitable solvent, and the resulting salt may then be isolated either by filtration of by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts can be obtained in an analogous manner by treating a solution of a compound of formula I with the appropriate base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

The above procedures may be adapted as appropriate to the particular reactants and groups involved and other variants will be evident to the skilled chemist by reference to standard textbooks and to the examples provided hereafter to enable all of the compounds of formula I to be prepared.

The compounds of the invention are useful because they possess pharmacological activity in animals, especially mammals including humans. They are therefore indicated as pharmaceuticals and, in particular, for use as animal medicaments.

According to a further aspect of the invention there is provided the compounds of the invention for use as medicaments, such as pharmaceuticals and animal medicaments.

By the term "treatment", we include both therapeutic (curative) or prophylactic treatment.

In particular, the compounds of the invention have been found to be useful in the treatment of diseases mediated *via* opiate receptors, which diseases

include irritable bowel syndrome; constipation; nausea; vomiting; pruritus; and conditions characterised by pruritus as a symptom.

Thus, according to a further aspect of the invention there is provided the use of the compounds of the invention in the manufacture of a medicament for the treatment of a disease mediated *via* an opiate receptor. There is further provided the use of the compounds of the invention in the manufacture of a medicament for the treatment of irritable bowel syndrome; constipation; nausea; vomiting; pruritus or a medical condition characterised by pruritus as a symptom.

The compounds of the invention are thus expected to be useful for the curative or prophylactic treatment of pruritic dermatoses including allergic dermatitis and atopy in animals and humans. Other diseases and conditions which may be mentioned include contact dermatitis, psoriasis, eczema and insect bites.

Thus, the invention provides a method of treating or preventing a disease mediated *via* an opiate receptor. There is further provided a method of treating irritable bowel syndrome; constipation; nausea; vomiting; pruritus or a medical condition characterised by pruritus as a symptom in an animal (e.g. a mammal), which comprises administering a therapeutically effective amount of a compound of the invention to an animal in need of such treatment.

The compounds of the invention will normally be administered orally or by any parenteral route, in the form of pharmaceutical preparations comprising the active ingredient, optionally in the form of a non-toxic

organic, or inorganic, acid, or base, addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated, as well as the route of administration, the compositions may be administered at varying doses (see below).

While it is possible to administer a compound of the invention directly without any formulation, the compounds are preferably employed in the form of a pharmaceutical, or veterinary, formulation comprising a pharmaceutically, or veterinarily, acceptable carrier, diluent or excipient and a compound of the invention. The carrier, diluent or excipient may be selected with due regard to the intended route of administration and standard pharmaceutical, and/or veterinary, practice. Pharmaceutical compositions comprising the compounds of the invention may contain from 0.1 percent by weight to 90.0 percent by weight of the active ingredient.

The methods by which the compounds may be administered for veterinary use include oral administration by capsule, bolus, tablet or drench, topical administration as an ointment, a pour-on, spot-on, dip, spray, mousse, shampoo, collar or powder formulation or, alternatively, they can be administered by injection (e.g. subcutaneously, intramuscularly or intravenously), or as an implant. Such formulations may be prepared in a conventional manner in accordance with standard veterinary practice.

The formulations will vary with regard to the weight of active compound contained therein, depending on the species of animal to be treated, the severity and type of infection and the body weight of the animal. For parenteral, topical and oral administration, typical dose ranges of the

active ingredient are 0.01 to 100 mg per kg of body weight of the animal. Preferably the range is 0.1 to 10 mg per kg.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg, more usually about 5 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discreet units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

In any event, the veterinary practitioner, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which may vary with the species, age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

For veterinary use, the compounds of the invention are of particular value for treating pruritus in domestic animals such as cats and dogs and in horses.

As an alternative for treating animals, the compounds may be administered with the animal feedstuff and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed.

For human use, the compounds are administered as a pharmaceutical formulation containing the active ingredient together with a pharmaceutically acceptable diluent or carrier. Such compositions include conventional tablet, capsule and ointment preparations which are formulated in accordance with standard pharmaceutical practice.

Compounds of the invention may be administered either alone or in combination with one or more agents used in the treatment or prophylaxis of disease or in the reduction or suppression of symptoms. Examples of such agents (which are provided by way of illustration and should not be construed as limiting) include antiparasitics, e.g. fipronil, lufenuron, imidacloprid, avermectins (e.g. abamectin, ivermectin, doramectin), milbemycins, organophosphates, pyrethroids; antihistamines, e.g. chlorpheniramine, trimeprazine, diphenhydramine, doxylamine; antifungals, e.g. fluconazole, ketoconazole, itraconazole, griseofulvin, amphotericin B; antibacterials, e.g. enroflaxacin, marbofloxacin, ampicillin, amoxycillin; anti-inflammatories e.g. prednisolone, betamethasone, dexamethasone, carprofen, ketoprofen; dietary supplements, e.g. gamma-linoleic acid; and emollients. Therefore, the invention further provides a product containing a compound of the invention and a compound from the above list as a combined preparation for simultaneous, separate or sequential use in the treatment of diseases mediated *via* opiate receptors.

The skilled person will also appreciate that compounds of the invention may be taken as a single dose on an "as required" basis (i.e. as needed or desired).

Thus, according to a further aspect of the invention there is provided a pharmaceutical, or veterinary, formulation including a compound of the invention in admixture with a pharmaceutically, or veterinarily, acceptable adjuvant, diluent or carrier.

Compounds of the invention may also have the advantage that, in the treatment of human and/or animal patients, they may be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, be more easily absorbed than, or they may have other useful pharmacological properties over, compounds known in the prior art.

The biological activities of the compounds of the present invention were determined by the following test method.

Biological Test

Compounds of the present invention have been found to display activity in binding assays selective for the mu opioid receptor in dog brain. The assays were conducted by the following procedure.

Laboratory bred beagles were used as a source of dog brain tissue. Animals were euthanised, their brains removed and the cerebellum discarded. The remaining brain tissue was sectioned into small pieces approximately 3 g in weight and homogenised in 50 mM Tris pH 7.4 buffer at 4°C using a Kinematica Polytron™ tissue homogeniser. The resulting homogenate was centrifuged at 48,400 x g for 10 minutes and the supernatant discarded. The pellet was resuspended in Tris buffer and

incubated at 37°C for 10 minutes. Centrifugation, resuspension and incubation steps were repeated twice more, and the final pellet was resuspended in Tris buffer and stored at -80°C. Membrane material prepared in this manner could be stored for up to four weeks prior to use.

For mu assays, increasing concentrations of experimental compound, (5 x 10^{-12} to 10^{-5} M), Tris buffer and ^{3}H ligand, ([D-Ala^2,N-Me-Phe^4,Gly-ol^5]-Enkephalin, DAMGO), were combined in polystyrene tubes. The reaction was initiated by the addition of tissue, and the mixture was incubated at room temperature for 90 minutes. The reaction was terminated by rapid filtration using a Brandel Cell Harvester™ through Betaplate™ GF/A glass fibre filters pre-soaked in 50 mM Tris pH 7.4, 0.1% polyethylenimine buffer. The filters were then washed three times with 0.5 mL ice-cold Tris pH 7.4 buffer. Washed filters were placed in bags and Starscint™ scintillant added. Bags containing the filters and scintillant were heat sealed and counted by a Betaplate™ 1204 beta counter.

Duplicate samples were run for each experimental compound and the data generated was analysed using IC_{50} analysis software in Graphpad Prism. Ki values were calculated using Graphpad Prism according to the following formula:

$$Ki = IC_{50} / 1 + [^3H \text{ ligand}] / K_D$$

where IC_{50} is the concentration at which 50% of the ^{3}H ligand is displaced by the test compound and K_D is the dissociation constant for the ^{3}H ligand at the receptor site.

The invention is illustrated by the following Preparations and Examples in which the following abbreviations may be used:

APCI = atmospheric pressure chemical ionisation
br (in relation to NMR) = broad
DMF = *N*,*N*-dimethylformamide
DMSO = dimethylsulfoxide
d (in relation to time) = day
d (in relation to NMR) = doublet
dd (in relation to NMR) = doublet of doublets
EtOAc = ethyl acetate
EtOH = ethanol
h = hour(s)
m (in relation to NMR) = multiplet
MeOH = methanol
min = minute
q (in relation to NMR) = quartet
s (in relation to NMR) = singlet
t (in relation to NMR) = triplet
THF = tetrahydrofuran

When reverse phase HPLC is mentioned in the text the following 2 sets of conditions were employed.

Condition 1: A Phenomenex Magellen™ column, 150 x 21 mm, packed with 5m C_{18} silica, eluting with a gradient of acetonitrile : 0.1 M aqueous

ammonium acetate (30:70 to 95:5 over 10 mins, flow rate 20 mL per minute).

Condition 2: A Dynamax™ column, 42 x 250 mm, packed with 8μ C_{18} silica, eluting with acetonitrile : 0.1 M aqueous ammonium acetate (30:70) at 45 mL per minute.

In both cases, combination and evaporation of appropriate fractions, determined by analytical HPLC, provided the desired compounds as acetate salts.

Analytical HPLC conditions used to highlight appropriate fractions were Phenomenex Magellan™ column, 4.6 x 150 mm, packed with 5μ C_{18} silica, eluting with a gradient of acetonitrile : 0.1 M aqueous heptanesulfonic acid (10:90 to 90:10 over 30 min, followed by a further 10 min at 90:10) at 1 mL per minute. Column oven temperature was 40°C, and ultraviolet detection of components was made at 220 nM.

When column chromatography is referred to this usually refers to a glass column packed with silica gel (40-63 μm). Pressure of ~165 kPa is generally applied and the ratio of crude product : silica gel required for purification is typically 50:1. Alternatively, an Isolute™ SPE (solid phase extraction) column or Waters Sep-Pak™ cartridge packed with silica gel may be used under atmospheric pressure. The ratio of crude product to silica gel required for purification is typically 100:1.

The hydrochloride salt may be made by methods commonly known to those skilled in the art of synthetic chemistry. Typically, to a solution of

free base in dichloromethane (1 g : 100 mL) was added ethereal hydrochloric acid (1.0 M, 1.2 equivalent), the excess solvent was decanted off and the remaining precipitate was washed three times with ether and then dried *in vacuo*.

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. ^{1}H Nuclear magnetic resonance (NMR) spectral data were obtained using a Varian Unity 300 or 400 spectrometer, the observed chemical shifts (δ) being consistent with the proposed structures. Mass spectral (MS) data were obtained on a Fisons Instruments Trio 1000, or a Fisons Instruments Trio 1000 APCI, or a Finnigan Navigator MS, or a Micromass Platform LC spectrometer. The calculated and observed ions quoted refer to the isotopic composition of lowest mass. HPLC means high performance liquid chromatography. Room temperature means 20 to 25°C.

Examples

Example 1: 1-Hexyl-3,4-dimethyl-4-(3-cyanophenyl)piperidine

A solution of 1-hexyl-3,4-dimethyl-4-(3-trifluoromethanesulfonyloxy-phenyl)piperidine (Preparation 1, 500 mg, 1.19 mmol) in 1-methyl-2-pyrrolidinone (2.5 mL) was added to a flask containing potassium cyanide (155 mg, 2.38 mmol). The solution was de-oxygenated by evacuating and flushing with nitrogen three times. Catalytic quantities of palladium(II) acetate and 1,1'-bis(diphenylphosphino)ferrocene were added and the reaction mixture was warmed to 60°C, at which temperature it was stirred for 3 hours. The reaction mixture was cooled to room temperature and poured into saturated aqueous sodium hydrogencarbonate solution

(50 mL). The product was extracted into ethyl acetate (3 x 30 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (15 g) eluted with a gradient of ethyl acetate : hexane : 0.880 ammonia (20:79:1 to 50:49:1) to give the title compound as an oil (346 mg).

NMR ($CDCl_3$) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (m, 1H), 2.0 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 7.35-7.6 (m, 4H).

MS (electrospray) : M/Z (MH^+) 299.2; $C_{20}H_{30}N_2$ + H requires 299.2.

Example 2: 1-Hexyl-3,4-dimethyl-4-(3-amidophenyl)piperidine

A mixture of polyphosphoric acid (160 mg) and 1-hexyl-3,4-dimethyl-4-(3-cyanophenyl)piperidine (Example 1, 19 mg, 0.064 mmol) was heated at 115°C for one hour. The reaction mixture was then cooled to room temperature and diluted with iced water (0.4 mL). Aqueous sodium hydroxide solution (2 *N*) was added until the pH was 7. The mixture was extracted with ethyl acetate (3 x 10 mL). The combined organics were dried (Na_2SO_4) and the solvent evaporated *in vacuo* to give a white solid. Purification by column chromatography on silica gel (1 g) eluted with ethyl acetate : ethanol : 0.880 ammonia (89:10:1) gave the product as a white solid (6 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.6 (m, 2H), 2.8 (m, 1H), 7.35 (t, 1H), 7.45 (d, 1H), 7.55 (d, 1H), 7.8 (s, 1H).

MS (electrospray) : M/Z (MH^+) 317.3; $C_{20}H_{32}N_2O$ + H requires 317.3.

Example 3: 1-Hexyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)-piperidine

To a stirred solution of 1-hexyl-3,4-dimethyl-4-(3-trifluoromethane-sulfonyloxyphenyl)piperidine (Preparation 1, 500 mg, 1.19 mmol) in anhydrous *N*,*N*-dimethylformamide (6 mL) was added triethylamine (1.7 mL, 12.2 mmol) and anhydrous methanol (1.0 mL, 24.7 mmol). The solution was de-oxygenated by evacuating and flushing with nitrogen five times. Palladium(II) acetate (27 mg, 0.12 mmol) and 1,1'-bis(diphenyl-phosphino)ferrocene (67 mg, 0.12 mmol) were added and the mixture was de-oxygenated again, using the same procedure as before. Carbon monoxide gas was bubbled through the mixture for 5 minutes and it was then stirred under an atmosphere of carbon monoxide and heated at 120°C overnight. The solvent was removed *in vacuo* to give a brown oil (0.7 g) which was purified by column chromatography on silica gel (35 g) eluted with a gradient of ethyl acetate : hexane : 0.880 ammonia (10:190:1 to 10:90:1 to 25:75:1). This gave the title compound as a yellow oil (250 mg).

NMR ($CDCl_3$) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m containing s, 9H), 1.4-1.55 (m, 2H), 1. 7 (m, 1H), 2.1 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.6 (m, 2H), 2.8 (m, 1H), 3.9 (s, 3H), 7.35 (t, 1H), 7.5 (d, 1H), 7.85 (d, 1H), 8.0 (s, 1H).

MS (APCI) : M/Z (MH^+) 332.4; $C_{21}H_{33}NO_2$ + H requires 332.3.

Example 4: 1-Hexyl-3,4-dimethyl-4-(3-(*N*-isopropyl)amidophenyl)-piperidine

In a sealed Wheaton™ vial, 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonyl-phenyl)piperidine (Example 3, 40 mg, 0.12 mmol) and isopropylamine (5 mL, 59 mmol) were heated together at 150°C for two days. The

reaction mixture was then cooled to room temperature and excess amine was removed by evaporation *in vacuo*. The residue was purified by column chromatography on silica gel (5 g) eluted with ethyl acetate : ethanol : 0.880 ammonia (50:49:1) to give the title compound as an oil (32 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 15H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.85 (m, 1H), 4.3 (m, 1H) 7.3-7.5 (m, 3H), 7.75 (s, 1H).

MS (electrospray) : M/Z (MH^+) 359.3; $C_{23}H_{38}N_2O$ + H requires 359.3.

Example 5: 1-Hexyl-3,4-dimethyl-4-(3-(*N*-butyl)amidophenyl)-piperidine

In a sealed Wheaton™ vial, 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonyl-phenyl)piperidine (Example 3, 30 mg, 0.09 mmol) and *n*-butylamine (4 mL, 40.5 mmol) were heated together at 140°C for two days. The reaction mixture was then cooled to room temperature and excess amine was removed by evaporation *in vacuo*. The residue was purified by column chromatography on silica gel (5 g) eluted with ethyl acetate : hexane : 0.880 ammonia (40:49:1) to give the title compound as an oil (20 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 0.95 (t, 3H), 1.2-1.8 (m, 16H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.85 (m, 1H), 3.45 (m, 2H), 7.3-7.55 (m, 3H), 7.75 (s, 1H).

MS (electrospray) : M/Z (MH^+) 373.3; $C_{24}H_{40}N_2O$ + H requires 373.3.

Example 6: 1-Hexyl-3,4-dimethyl-4-(3-(*N*-propyl)amidophenyl)-piperidine

In a sealed Wheaton™ vial, 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonyl-phenyl)piperidine (Example 3, 30 mg, 0.09 mmol) and *n*-propylamine (4 mL, 94 mmol) were heated together at 140°C for two days. The reaction mixture was then cooled to room temperature and excess amine was removed by evaporation *in vacuo*. The residue was purified by column chromatography on silica gel (5 g) eluted with ethyl acetate : ethanol : 0.880 ammonia (50:49:1) to give the title compound as an oil (3.5 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 1.0 (t, 3H), 1.25-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6-1.75 (m, 3H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 3.45 (m, 2H), 7.3-7.5 (m, 3H), 7.75 (s, 1H).

MS (electrospray) : M/Z (MH^+) 359.3; $C_{23}H_{38}N_2O$ + H requires 359.3.

Example 7: 1-Hexyl-3,4-dimethyl-4-(3-(*N*-benzyl)amidophenyl)-piperidine

In a sealed Wheaton™ vial, 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonyl-phenyl)piperidine (Example 3, 30 mg, 0.09 mmol) and benzylamine (3 mL, 27.5 mmol) were heated together at 100°C for 76 hours. The reaction mixture was cooled to room temperature, concentrated and the residue purified by column chromatography on silica gel eluted with a gradient of hexane : ethyl acetate (20:80 to 50:50). The title compound was obtained as a pale oil (13 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (t, 3H), 1.2-1.4 (m, 9H), 1.6-1.55 (m, 2H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-

2.65 (m, 2H), 2.85 (m, 1H), 4.65 (m, 2H), 7.3-7.4 (m, 6H), 7.45 (d, 1H), 7.55 (d, 1H), 7.8 (s, 1H).

MS (electrospray) : M/Z (MH^+) 407.3; $C_{27}H_{38}N_2O$ + H requires 407.3.

Example 8: 1-Hexyl-3,4-dimethyl-4-(3-(*N*-ethyl)amidophenyl)-piperidine

In a sealed Wheaton™ vial, 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonyl-phenyl)piperidine (Example 3, 30 mg, 0.09 mmol) and ethylamine (3 mL, 45.8 mmol) were heated together at 100°C for 60 hours. The ethylamine was found to be evaporating, thus the reaction mixture was transferred to a sealed bomb and heated at 100°C and 690 kPa for a further 16 hours. The reaction mixture was cooled to room temperature, concentrated and then purified by column chromatography on silica gel eluted with a gradient of hexane : ethyl acetate (20:80 to 50:50). The title compound was obtained as a pale oil (11 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 12H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.85 (m, 1H), 3.5 (m, 2H), 7.35 (t, 1H), 7.4 (d, 1H), 7.5 (d, 1H), 7.75 (s, 1H).

MS (thermospray) : M/Z (MH^+) 345.1 $C_{22}H_{36}N_2O$ + H requires 345.3.

Example 9: 1-Hexyl-3,4-dimethyl-4-(3-(*N*-isobutyl)amidophenyl)-piperidine

The title compound was prepared by the method of Example 7, substituting benzylamine with isobutylamine (3 mL, 30.18 mmol). This gave the title compound as a pale oil (9 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (t, 3H), 1.0 (d, 6H), 1.2-1.35 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 1.9 (m, 1H), 2.05 (m,

1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 3.3, (t, 2H), 7.35 (t, 1H), 7.45 (d, 1H), 7.5 (d, 1H), 7.75 (s, 1H).

MS (electrospray) : M/Z (MH^+) 373.3; $C_{24}H_{40}N_2O$ + H requires 373.3.

Example 10: 1-Hexyl-3,4-dimethyl-4-{3-[*N*-(2-methoxyethyl)]-amidophenyl}piperidine

In a sealed Wheaton™ vial, 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonyl-phenyl)piperidine (Example 3, 30 mg, 0.09 mmol) and 2-methoxy-ethylamine (3 mL, 34.5 mmol) were heated together at 130°C for 120 hours. The reaction mixture was cooled to room temperature, concentrated and purified by column chromatography on silica gel eluted with a gradient of hexane : ethyl acetate : 0.880 ammonia gradient (10:89:1 to 49:50:1). The gave the title compound as a pale oil (8 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 3.3-3.7 (m, 7H), 7.35 (t, 1H), 7.4 (d, 1H), 7.5 (d, 1H), 7.75 (s, 1H).

MS (APCI) : M/Z (MH^+) 374.5; $C_{23}H_{38}N_2O_2$ + H requires 374.3.

Example 11: 1-Hexyl-3,4-dimethyl-4-(3-(*N*-methyl)amidophenyl)-piperidine

To a suspension of anhydrous methylamine hydrochloride (17 mg, 0.25 mmol) in anhydrous toluene (0.5 mL) stirred under nitrogen and cooled in an ice bath was added a solution of trimethylaluminium (2.0 M in toluene, 0.12 mL, 0.24 mmol). The mixture was allowed to warm to room temperature while stirring for 4 hours, then it was treated with a solution of 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)piperidine (Example 3, 40 mg, 0.12 mmol) in anhydrous toluene (1.5 mL). The

resulting mixture was heated at reflux overnight, then quenched with dilute hydrochloric acid (10 mL of 2 *N*) and extracted with diethyl ether (10 mL). The aqueous phase was basified to pH 13 with aqueous sodium hydroxide solution (2 *N*) and extracted with dichloromethane (3 x 20 mL). The combined dichloromethane extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give an orange oil (31 mg) which was purified by column chromatography on silica gel (1.2 g) eluted with ethyl acetate : hexane : 0.880 ammonia (50:50:1). This gave the title compound as a colourless residue (17 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 3.0 (d, 3H), 7.35 (t, 1H), 7.4 (d, 1H), 7.5 (d, 1H), 7.75 (s, 1H).

MS (APCI) : M/Z (MH^+) 331.1; $C_{21}H_{34}N_2O$ + H requires 331.3.

Example 12: 1-Hexyl-3,4-dimethyl-4-(3-(*N*,*N*-dimethyl)amidophenyl)-piperidine

The title compound was prepared as for Example 11 except using anhydrous dimethylamine hydrochloride (20 mg, 0.25 mmol) in place of methylamine hydrochloride. This gave a pale yellow oil (38 mg).

NMR ($CDCl_3$) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.0 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 2.95 (br s, 3H), 3.1 (br s, 3H), 7.15-7.25 (m, 1H), 7.25-7.4 (m, 3H).

MS (thermospray) : M/Z (MH^+) 345.2; $C_{22}H_{36}N_2O$ + H requires 345.3.

Example 13: 1-Hexyl-3,4-dimethyl-4-(3-(*N*,*N*-diethyl)amidophenyl)-piperidine

To a suspension of anhydrous diethylamine hydrochloride (30 mg, 0.27 mmol) in anhydrous toluene (0.5 mL) stirred under nitrogen and cooled in an ice bath was added a solution of trimethylaluminium (2.0 M in toluene, 0.14 mL, 0.28 mmol). The mixture was allowed to warm to room temperature while stirring for 2 hours, then it was treated with a solution of 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)piperidine (Example 3, 44 mg, 0.13 mmol) in anhydrous toluene (1 mL). The resulting mixture was heated at reflux for 2½ days, then quenched with dilute hydrochloric acid (10 mL of 2 *N*) and extracted with diethyl ether (10 mL). The aqueous phase was basified to pH 13 with aqueous sodium hydroxide solution (2 *N*) and extracted with dichloromethane (3 x 20 mL). The combined dichloromethane extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give an orange oil (52 mg) which was purified by column chromatography on silica gel (1.5 g) eluted with a gradient of ethyl acetate : hexane : 0.880 ammonia (10:90:1 to 20:40:1). This gave the title compound as a yellow oil (34 mg).

NMR ($CDCl_3$) : 0.75 (d, 3H), 0.9 (m, 3H), 1.0-1.4 (m, 15H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.0 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 3.25 (br m, 2H), 3.55 (br m, 2H), 7.1-7.2 (m, 1H), 7.2-7.35 (m, 3H).

MS (APCI) : M/Z (MH^+) 373.1; $C_{24}H_{40}N_2O$ + H requires 373.3.

Example 14: 1-Hexyl-3,4-dimethyl-4-(3-(*N*-*tert*-butyl)amidophenyl)-piperidine

A solution of 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)-piperidine (Example 3, 40 mg, 0.12 mmol) in dilute hydrochloric acid

(5 mL of 2 *N*) was heated at reflux overnight. The solvent was removed *in vacuo* and the residue was taken up in methanol and re-concentrated *in vacuo* to give a brown oil (40 mg) which was dissolved in dichloromethane (1 mL) and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (25 mg, 0.13 mmol), *N*-methylmorpholine (27 μL, 0.25 mmol) and *tert*-butylamine (14 μL, 0.13 mmol). The resulting mixture was stirred at room temperature overnight, then poured into saturated aqueous sodium hydrogencarbonate solution (5 mL) and extracted with dichloromethane (3 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a brown residue which was purified by column chromatography on silica gel (2.5 g) eluted with a gradient of ethyl acetate : hexane : 0.880 ammonia (5:95:1 to 10:90:1 to 20:80:1 to 30:70:1). This gave the title compound as a colourless residue (10 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 11H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.6 (m, 2H), 2.8 (m, 1H), 7.3-7.45 (m, 3H), 7.75 (s, 1H).

MS (APCI) : M/Z (MH^+) 373.1; $C_{24}H_{40}N_2O$ + H requires 373.3.

Example 15: 1-Benzyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)-piperidine

A stirred solution of 1-benzyl-3,4-dimethyl-4-(3-trifluoromethanesulfonyloxyphenyl)piperidine (Preparation 2, 506 mg, 1.18 mmol), triethylamine (1.6 mL, 11.8 mmol) and anhydrous methanol (1.9 mL, 46.8 mmol) in anhydrous *N*,*N*-dimethylformamide (6 mL) was de-oxygenated by evacuating and flushing with nitrogen five times. Palladium(II) acetate (30 mg, 0.13 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (63 mg, 0.11 mmol) were added and the mixture was

again de-oxygenated, using the same method as before. Carbon monoxide gas was bubbled through the mixture for *ca* 5 minutes and it was subsequently heated at 80°C under an atmosphere of carbon monoxide overnight. The mixture was then poured into water (100 mL) and extracted with diethyl ether (3 x 100 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give an orange oil (250 mg). A black residue remaining in the reaction flask, insoluble in diethyl ether, was dissolved in dichloromethane and transferred to the separating funnel containing the aqueous layer and this was re-extracted with dichloromethane (3 x 50 mL). The combined organics were filtered through Celite® to remove residual palladium, dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil (270 mg). The combined oils were purified by silica (25 g) column chromatography eluting with a gradient of hexane : ethyl acetate : 0.880 ammonia (140:10:1 to 90:10:1) to give the title compound as a colourless oil (335 mg).

NMR ($CDCl_3$) : 0.75 (d, 3H), 1.35 (s, 3H), 1.65 (m, 1H), 2.05 (m, 1H), 2.3-2.5 (m, 2H), 2.5-2.65 (m, 2H), 2.85 (m, 1H), 3.45 (d, 1H), 3.6 (d, 1H), 3.9 (s, 3H), 7.2-7.4 (m, 6H), 7.5 (d, 1H), 7.85 (d, 1H), 8.0 (s, 1H).

MS (thermospray) : M/Z (MH^+) 338.2; $C_{22}H_{27}NO_2$ + H requires 338.2.

Example 16: 1-Benzyl-3,4-dimethyl-4-(3-(*N*-ethyl)amidophenyl)-piperidine

A stirred suspension of ethylamine hydrochloride (880 mg, 10.8 mmol) in anhydrous toluene (10 mL) was de-oxygenated by evacuating and flushing with nitrogen three times. Stirring under nitrogen it was cooled in an ice bath and treated with trimethylaluminium solution (2.0 M in toluene, 5.4 mL, 10.8 mmol) via syringe. The mixture was allowed to warm to room temperature while stirring for 1¼ hours. A solution of 1-benzyl-

3,4-dimethyl-4-(3-methoxycarbonylphenyl)piperidine (Example 15, 1.81 g, 5.36 mmol) in anhydrous toluene (20 mL) was added via syringe and the reaction mixture was heated at reflux overnight. After it had cooled, aqueous hydrochloric acid (100 mL of 2 *N*) was added and the mixture was extracted with diethyl ether (100 mL). The organic extract was back-washed with aqueous hydrochloric acid (50 mL of 2 *N*). The combined aqueous phases were basified to pH 13 with aqueous sodium hydroxide solution (2 *N*) and then extracted with dichloromethane (300 mL followed by 2 x 100 mL). The combined dichloromethane extracts were washed with water (150 mL) followed by saturated aqueous sodium chloride solution (150 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil (2.0 g). Purification by silica (100 g) column chromatography eluting with a gradient of ethyl acetate : hexane : 0.880 ammonia (20:80:1 to 30:70:1 to 40:60:1) gave the title compound as a cream foam (805 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 1.25 (t, 3H), 1.35 (s, 3H), 1.65 (m, 1H), 2.05 (m, 1H), 2.35-2.45 (m, 2H), 2.5-2.6 (m, 2H), 2.85 (m, 1H), 3.4-3.55 (m, 3H), 3.6 (d, 1H), 7.2-7.35 (m, 6H), 7.4 (d, 1H), 7.5 (d, 1H), 7.75 (s, 1H).

MS (APCI) : M/Z (MH^+) 351.3; $C_{23}H_{30}N_2O$ + H requires 351.2.

Example 17: 1-(2-Phenoxyethyl)-3,4-dimethyl-4-(3-(*N*-ethyl)-amidophenyl)piperidine

A stirred mixture of 3,4-dimethyl-4-(3-(*N*-ethyl)amidophenyl)piperidine (Preparation 3, 50 mg, 0.19 mmol), 2-bromoethyl phenyl ether (42 mg, 0.20 mmol), and sodium hydrogencarbonate (19.1 mg, 0.22 mmol) in anhydrous *N*,*N*-dimethylformamide (1 mL) was heated at 100°C for 2 hours. The solvent was then removed *in vacuo* to give a brown oil

which was purified by column chromatography on silica gel (4 g) eluted initially with CH_2Cl_2, changing incrementally to CH_2Cl_2 : MeOH (25:1), to give the title compound as a yellow oil (55 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 1.25 (t, 3H), 1.35 (s, 3H), 1.65 (m, 1H), 2.05 (m, 1H), 2.35 (m, 1H), 2.55 (m, 1H), 2.6-2.8 (m, 3H), 2.8-2.95 (m, 2H), 3.5 (m, 2H), 4.1 (m, 2H), 6.9-7.0 (m, 3H), 7.3 (m, 2H), 7.35 (m, 1H), 7.4 (m, 1H), 7.5 (d, 1H), 7.75 (s, 1H).

MS (thermospray) : M/Z (MH^+) 381.2; $C_{24}H_{32}N_2O_2$ + H requires 381.3.

Example 18: 1-(5-Methylhexyl)-3,4-dimethyl-4-(3-(*N*-ethyl)-amidophenyl)piperidine

A stirred mixture of 3,4-dimethyl-4-(3-(*N*-ethyl)amidophenyl)piperidine (Preparation 3, 50 mg, 0.19 mmol), 1-bromo-5-methylhexane (37 mg, 0.20 mmol), and sodium hydrogencarbonate (19.1 mg, 0.22 mmol) in anhydrous *N*,*N*-dimethylformamide (1 mL) was heated at 100°C for 2½ hours. The solvent was then removed *in vacuo* to give a brown oil which was purified by column chromatography on silica gel (4 g) eluted initially with CH_2Cl_2, changing incrementally to CH_2Cl_2 : MeOH (25:1), to give the title compound as a yellow oil (58 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.85 (d, 6H), 1.15 (m, 2H), 1.2-1.35 (m, 8H), 1.35-1.6 (m, 3H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.85 (m, 1H), 3.5 (m, 2H), 7.35 (t, 1H), 7.4 (d, 1H), 7.5 (d, 1H), 7.75 (s, 1H).

MS (thermospray) : M/Z (MH^+) 359.5; $C_{23}H_{38}N_2O$ + H requires 359.3.

Example 19: 1-(3-Phenylpropyl)-3,4-dimethyl-4-(3-(*N*-ethyl)-amidophenyl)piperidine

A stirred mixture of 3,4-dimethyl-4-(3-(*N*-ethyl)amidophenyl)piperidine (Preparation 3, 50 mg, 0.19 mmol), 1-bromo-3-phenylpropane (32 μL, 0.21 mmol), and sodium hydrogencarbonate (19.1 mg, 0.22 mmol) in anhydrous *N*,*N*-dimethylformamide (1 mL) was heated at 100°C for 2 hours. The solvent was then removed *in vacuo* to give a brown oil which was purified by column chromatography on silica gel (4 g) eluted initially with CH_2Cl_2, changing incrementally to CH_2Cl_2 : MeOH (25:1), followed by further purification by column chromatography on silica gel (4 g) eluted with a gradient of CH_2Cl_2 : MeOH (50:1 to 50:2). This gave the title compound as a yellow oil (55 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 1.25 (t, 3H), 1.3 (s, 3H), 1.65 (m, 1H), 1.8 (m, 2H), 2.05 (m, 1H), 2.25-2.45 (m, 4H), 2.45-2.7 (m, 4H), 2.85 (m, 1H), 3.5 (m, 2H), 7.15-7.2 (m, 3H), 7.25 (m, 2H), 7.35 (t, 1H), 7.4 (d, 1H), 7.5 (d, 1H), 7.75 (s, 1H).

MS (thermospray) : M/Z (MH^+) 379.0; $C_{25}H_{34}N_2O$ + H requires 379.3.

Example 20: 1-(5-Cyanopentyl)-3,4-dimethyl-4-(3-(*N*-ethyl)-amidophenyl)piperidine

A stirred mixture of 3,4-dimethyl-4-(3-(*N*-ethyl)amidophenyl)piperidine (Preparation 3, 50 mg, 0.19 mmol), 6-bromohexanenitrile (28 μL, 0.20 mmol), and sodium hydrogencarbonate (19.1 mg, 0.22 mmol) in anhydrous *N*,*N*-dimethylformamide (1 mL) was heated at 100°C for 4 hours. The solvent was then removed *in vacuo* to give a brown oil which was purified by column chromatography on silica gel (4 g) eluted initially with CH_2Cl_2, changing incrementally to CH_2Cl_2 : MeOH (25:1), to give a yellow oil (82 mg), followed by further purification by column

chromatography on silica gel (4 g) eluted with a gradient of CH_2Cl_2 : MeOH (50:1 to 50:2). This gave the title compound as a yellow oil (54 mg).

NMR ($CDCl_3$, selected data) : 0.8 (d, 3H), 1.25 (t, 3H), 1.35 (s, 3H), 1.5 (m, 2H), 1.55-1.8 (m, 5H), 2.15 (m, 1H), 2.35 (t, 2H), 2.4-2.6 (m, 4H), 2.6-2.75 (m, 2H), 2.95 (m, 1H), 3.5 (m, 2H), 7.3-7.45 (m, 2H), 7.5 (d, 1H), 7.75 (s, 1H).

MS (thermospray) : M/Z (MH^+) 356.4; $C_{22}H_{33}N_3O$ + H requires 356.3.

Example 21: 1-Hexyl-3,4-dimethyl-4-(3-aminomethylphenyl)piperidine

To a stirred solution of 1-hexyl-3,4-dimethyl-4-(3-cyanophenyl)piperidine (Example 1, 800 mg, 2.68 mmol) in anhydrous tetrahydrofuran (40 mL) at 0°C under nitrogen was added lithium aluminium hydride (1.0 M in tetrahydrofuran, 4.0 mL, 4.0 mmol). The reaction mixture was allowed to warm to room temperature, before being heated to 37°C for 30 minutes. Subsequently, diethyl ether (50 mL), then aqueous sodium hydroxide (0.3 mL, 15% w/v solution) and finally water (0.45 mL) were added. The white solid formed was filtered off. The filtrate was washed with saturated aqueous sodium hydrogencarbonate solution (2 x 50 mL). The aqueous phases were back-extracted with diethyl ether (50 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as an oil (770 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.0 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.6 (m, 2H), 2.8 (m, 1H), 3.85 (s, 2H), 7.1-7.35 (m, 4H).

MS (APCI) : M/Z (MH^+) 303.4; $C_{20}H_{34}N_2$ + H requires 303.3.

Example 22: 1-Hexyl-3,4-dimethyl-4-(3-(*N*-methoxycarbonyl)amino-methylphenyl)piperidine

To a stirred solution of 1-hexyl-3,4-dimethyl-4-(3-aminomethylphenyl)-piperidine (Example 21, 100 mg, 0.33 mmol) in pyridine (2 mL, dried over basic alumina) at 0°C under nitrogen was added methyl chloroformate (40 μL, 0.52 mmol). The reaction mixture was stirred at room temperature under a nitrogen atmosphere overnight. Subsequently, ice was added followed by aqueous sodium hydroxide (5 *N* solution) to give a pH of 11. The mixture was extracted with diethyl ether (3 x 25 mL). The combined organic phases was dried ($MgSO_4$) and then concentrated *in vacuo* at 70°C to give an oil (104 mg) which was purified by column chromatography on silica gel (2.9 g) eluted with a gradient of ethyl acetate : hexane (1:2 to 2:1). This gave the title compound as an oil (65 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.35 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (m, 1H), 2.0 (m, 1H), 2.2-2.4 (m, 4H), 2.4-2.6 (m, 2H), 2.8 (m, 1H), 3.7 (s, 3H), 4.35 (d, 2H), 7.1 (d, 1H), 7.15-7.35 (m, 3H).

MS (thermospray) : M/Z (MH^+) 361.4; $C_{22}H_{36}N_2O_2$ + H requires 361.3.

Example 23: 1-Hexyl-3,4-dimethyl-4-(3-(*N*-acetyl)aminomethylphenyl)-piperidine

This preparation was carried out using the procedure described for Example 22 except using acetyl chloride (35 μL, 0.49 mmol) in place of methyl chloroformate. This gave the title compound as an oil (100 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (m, 1H), 1.95-2.05 (m, 4H), 2.2-2.4 (m, 4H),

2.4-2.6 (m, 2H), 2.8 (m, 1H), 4.4 (d, 2H), 7.1 (d, 1H), 7.15-7.35 (m, 3H).

MS (APCI) : M/Z (MH^+) 345.3; $C_{22}H_{36}N_2O$ + H requires 345.3.

Example 24: 1-Hexyl-3,4-dimethyl-4-(3-(*N*-methanesulfonyl)amino-methylphenyl)piperidine

This preparation was carried out using the procedure described for Example 22 except using methanesulfonyl chloride (40 μL, 0.52 mmol) in place of methyl chloroformate. This gave the title compound as an oil (94 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (m, 1H), 2.0 (m, 1H), 2.2-2.4 (m, 4H), 2.4-2.65 (m, 2H), 2.75-2.9 (m, 4H), 4.3 (s, 2H), 7.15 (d, 1H), 7.2-7.35 (m, 3H).

MS (APCI) : M/Z (MH^+) 381.6; $C_{21}H_{36}N_2O_2S$ + H requires 381.3.

Example 25: 1-Hexyl-3,4-dimethyl-4-(3-(*N*-trifluoromethanesulfonyl)-aminomethylphenyl)piperidine

To a solution of 1-hexyl-3,4-dimethyl-4-(3-aminomethylphenyl)piperidine (Example 21, 100 mg, 0.33 mmol) in pyridine (1.5 mL, dried over basic alumina) stirred under nitrogen was added trifluoromethanesulfonyl chloride (0.3 mL, 0.28 mmol). The reaction mixture was stirred at room temperature under a nitrogen atmosphere overnight. Aqueous sodium hydroxide (20 mL of 2 *N*) was added and the mixture was extracted with dichloromethane (3 x 20 mL). The aqueous layer was treated with dilute aqueous hydrochloric acid (20 mL of 1 *N*) and then extracted with dichloromethane (2 x 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give an orange oil (40 mg) which

was purified by column chromatography on silica gel (1.2 g) eluted with a gradient of ethyl acetate : hexane : triethylamine (20:80:1) to ethyl acetate : triethylamine (100:1). This gave the title compound as an oil (30 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.75 (m, 6H), 2.8 (m, 1H), 4.4 (s, 2H), 7.15 (d, 1H), 7.2-7.35 (m, 3H).

MS (thermospray) : M/Z (MH^+) 435.1; $C_{21}H_{33}F_3N_2O_2S$ + H requires 435.2.

Example 26: 1-Hexyl-3,4-dimethyl-4-(3-vinylphenyl)piperidine

A solution of 1-hexyl-3,4-dimethyl-4-(3-trifluoromethanesulfonyloxy-phenyl)piperidine (Preparation 1, 1.5 g, 3.6 mmol) in 1,4-dioxan (17 mL) was de-oxygenated by evacuating and flushing with nitrogen five times. Vinyl tributyl tin (1.06 mL, 3.71 mmol) was added under stirring, followed by lithium chloride (456 mg, 10.76 mmol), tetrakis(triphenyl-phosphine)palladium(0) (catalytic) and 2,6-di-*tert*-butyl-4-methylphenol (2 crystals). The suspension was stirred under nitrogen and heated at reflux for ten hours. After cooling to room temperature the reaction mixture was quenched with aqueous ammonium hydroxide solution (50 mL, 1.0 M) and further diluted with ethyl acetate (50 mL). The phases were separated and the aqueous layer was further extracted with ethyl acetate (3 x 25 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. The residual oil was purified by column chromatography on silica gel (120 g) eluted with ethyl acetate: hexane: 0.880 ammonia (39:60:1) to give the title compound as an oil (890 mg).

NMR ($CDCl_3$) : 0.75 (d, 3H), 0.85 (m, 3H), 1.2-1.4 (m, 9H),1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m,

2H), 2.85 (m, 1H), 5.25 (d, 1H), 5.75 (d, 1H), 6.7 (dd, 1H), 7.1-7.35 (m, 4H).

MS (thermospray) : M/Z (MH^+) 300.4; $C_{21}H_{33}N$ + H requires 300.3.

Example 27: 1-Hexyl-3,4-dimethyl-4-(3-(1,2-dihydroxyethyl)phenyl)-piperidine

1-Hexyl-3,4-dimethyl-4-(3-vinylphenyl)piperidine (Example 26, 200 mg, 0.67 mmol) was dissolved in a mixture of water (2 mL) and acetone (18 mL). 4-methylmorpholine *N*-oxide (172 mg, 1.47 mmol) was added with stirring followed by osmium tetroxide (200 µL, 2.5% w/w in *tert*-butanol). The reaction mixture was stirred at room temperature for 4 hours before the solvent was removed by evaporation *in vacuo*. The residue was partitioned between dichloromethane (25 mL) and water (25 mL). The organic phase was separated and dried (Na_2SO_4). Concentration *in vacuo* gave a residue which was purified by column chromatography on silica gel (10 g) eluted with a gradient of ethyl acetate : hexane: ammonium hydroxide solution (50:49:1 to 60:33:1), followed by ethyl acetate: methanol: ammonium hydroxide solution (94:5:1). Combination of the appropriate fractions and evaporation to dryness *in vacuo* gave the product as a yellow oil (145 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 3.7 (m, 2H), 4.80 (m, 1H), 7.1-7.4 (m, 4H).

MS (thermospray) : M/Z (MH^+) 334.5; $C_{21}H_{35}NO_2$ + H requires 334.3.

Example 28: 1-Hexyl-3,4-dimethyl-4-(3-formylphenyl)piperidine

1-Hexyl-3,4-dimethyl-4-(3-vinylphenyl)piperidine (Example 26, 200 mg, 0.67 mmol) was dissolved in a mixture of water (2 mL) and acetone (18 mL). Osmium tetroxide (200 μL, 2.5% w/w in *tert*-butanol) was added, followed by sodium periodate (572 mg, 2.68 mmol) which was added portionwise. The reaction mixture was stirred at room temperature for 26 hours, then it was filtered to remove precipitate and the solvent was removed by evaporation *in vacuo*. The residue was partitioned between dichloromethane (25 mL) and saturated sodium chloride solution (25 mL). The organic phase was separated, dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica gel (50 g) eluted with ethyl acetate: hexane: 0.880 ammonia (74:25:1). The title compound was obtained as an oil (80 mg).

NMR ($CDCl_3$) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.6 (m, 2H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.85 (m, 1H), 7.5 (t, 1H), 7.55 (d, 1H), 7.7 (d, 1H), 7.8 (s, 1H), 10.0 (s, 1H).

MS (electrospray) : M/Z (MH^+) 302.0; $C_{20}H_{31}NO$ + H requires 302.2.

Example 29: 1-Hexyl-3,4-dimethyl-4-(3-(*N*-hydroxy)iminomethyl-phenyl)piperidine

A solution of 1-hexyl-3,4-dimethyl-4-(3-formylphenyl)piperidine (Example 28, 80 mg, 0.27 mmol) in a mixture of pyridine (1 mL) and ethanol (1 mL) was treated with hydroxylamine hydrochloride (22 mg, 0.32 mmol) and the resulting mixture was heated at reflux for 18 hours. The solvent was evaporated *in vacuo* and the residual orange oil was purified by column chromatography on silica gel (10 g) eluted with a

gradient of dichloromethane : methanol : 0.880 ammonia (98:1:1 to 94:5:1). This gave the title compound as an oil (18 mg).

NMR ($CDCl_3$, selected data) : 0.8 (d, 3H), 0.85 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.6 (m, 2H), 1.7 (m, 1H), 2.1 (m,1H), 2.2-2.75 (m, 6H), 2.95 (m, 1H), 7.2-7.4 (m, 3H), 7.6 (s, 1H), 8.1 (s, 1H).

MS (thermospray) : M/Z (MH^+) 317.6; $C_{20}H_{32}N_2O$ + H requires 317.3.

Example 30: 1-Hexyl-3,4-dimethyl-4-(3-acetylphenyl)piperidine

To a solution of 1-hexyl-3,4-dimethyl-4-(3-cyanophenyl)piperidine (Example 1, 791 mg, 2.65 mmol) in anhydrous tetrahydrofuran (6 mL) at 0°C was added methyl lithium (2.46 mL, 3.45 mmol) and the mixture darkened. The solution was then warmed to room temperature and stirred under a nitrogen atmosphere for 1 hour before being poured onto water (10 mL). The basic aqueous layer was extracted with diethyl ether : ethyl acetate (1:1, 3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. This gave the crude title compound as a colourless oil (720 mg, 86%).

NMR ($CDCl_3$) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.6 (m, 2H), 2.6 (s, 3H), 2.85 (m, 1H), 7.4 (t, 1H), 7.5 (d, 1H), 7.75 (d, 1H), 7.95 (s, 1H).

MS (thermospray) : M/Z (MH^+) 316.3; $C_{21}H_{33}NO$ + H requires 316.3.

Example 31: 1-Hexyl-3,4-dimethyl-4-(3-ethynylphenyl)piperidine

A solution of 1-hexyl-3,4-dimethyl-4-{3-[2-(trimethylsilyl)ethynyl]-phenyl}piperidine (Preparation 4, 150 mg, 0.40 mmol) in tetrahydrofuran (2 mL) was cooled to -70°C and tetrabutylammonium fluoride (1.0 M in THF, 0.41 mL, 0.41 mmol) was added slowly. The reaction mixture was

allowed to warm to room temperature gradually before being diluted with dichloromethane (10 mL) and water (10 mL). The phases were separated and the aqueous layer was further extracted with dichloromethane (2 x 10 mL). The combined organics were dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The oily yellow residue was purified by column chromatography on silica gel (10 g) eluted with ethyl acetate : hexane : 0.880 ammonia (10:89:1) to give the title compound as an oil (100 mg).

NMR ($CDCl_3$) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.35 (m, 9H), 1.35-1.55 (m, 2H), 1.6 (m, 1H), 2.0 (m, 1H), 2.2-2.6 (m, 6H), 2.8 (m, 1H), 3.05 (s, 1H), 7.2-7.35 (m, 3H), 7.45 (s, 1H).

MS (APCI) : M/Z (MH^+) 298.6; $C_{21}H_{31}N$ + H requires 298.3.

Example 32: 1-Hexyl-3,4-dimethyl-4-(3-(1,1-dimethyl)hydroxymethyl-phenyl)piperidine

A solution of 1-hexyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)-piperidine (Example 3, 50 mg, 0.15 mmol) in anhydrous tetrahydrofuran was de-oxygenated by evacuating and flushing with nitrogen three times. The solution was then cooled to 0°C and treated with methylmagnesium chloride (0.5 mL, 1.5 mmol, 3.0 M in tetrahydrofuran) dropwise. The reaction mixture was stirred at 50°C for 2 hours and then saturated aqueous ammonium chloride solution (20 mL) was added followed by saturated aqueous sodium hydrogencarbonate (20 mL). The mixture was extracted with ethyl acetate (3 x 15 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give an oil (39 mg). The residue was purified by column chromatography on silica gel (1 g) eluted with a gradient of ethyl acetate : hexane : ammonia (50:50:1 to 25:75:1) to give the title compound as a colourless oil (30 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 1.25-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (s, 6H), 1.65 (m, 1H), 2.05 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 7.15 (m, 1H), 7.2-7.3 (m, 2H), 7.45 (s, 1H).

MS (APCI) : M/Z (MH^+) 332.4; $C_{22}H_{37}NO$ + H requires 332.3.

Example 33: 1-Hexyl-3,4-dimethyl-4-(3-hydroxymethylphenyl)-piperidine

A stirred solution of 1-hexanoyl-3,4-dimethyl-4-(3-methoxycarbonyl-phenyl)piperidine (Preparation 7, 80 mg, 0.23 mmol) in anhydrous tetrahydrofuran (1 mL) under nitrogen was treated with lithium aluminium hydride (1.0 M in ether, 0.70 mL, 0.70 mmol) and the mixture was stirred at room temperature for 3 hours. The reaction mixture was then quenched with water (7.5 mL) and extracted with ethyl acetate (7 mL). The phases were separated and the aqueous layer was further extracted with ethyl acetate (2 x 5 mL). The combined organics were dried (Na_2SO_4) and the solvent removed *in vacuo* to give the title compound as a pale oil (30 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.65 (m, 1H), 2.0 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 4.7 (s, 2H), 7.1-7.35 (m, 4H).

MS (thermospray) : M/Z (MH^+) 304.3; $C_{20}H_{33}NO$ + H requires 304.3.

Example 34: 1-Hexyl-3,4-dimethyl-4-(3-(2-hydroxyethyl)phenyl)-piperidine

To a stirred solution of 1-hexanoyl-3,4-dimethyl-4-(3-vinylphenyl)-piperidine (Preparation 8, 50 mg, 0.16 mmol) in bis(2-methoxyethyl)ether (1.5 mL) at 0°C under nitrogen was added dropwise borane (1.0 M in

tetrahydrofuran, 0.35 mL, 0.35 mmol). The reaction mixture was stirred at 0°C for 30 minutes and then for 2 hours at room temperature. Trimethylamine *N*-oxide (48 mg, 0.64 mmol) was subsequently added and the reaction mixture heated at reflux under a nitrogen atmosphere for 2 hours. To the cooled reaction was then added diethyl ether (10 mL) and saturated aqueous sodium chloride solution (10 mL). The phases were separated and the aqueous layer was further extracted with diethyl ether (10 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (1.5 g) eluted with ethyl acetate : hexane (50:50) to give the title compound as an oil (30 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (m, 3H), 1.25-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (m, 1H), 2.0 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.6 (m, 2H), 2.8 (m, 1H), 2.85 (t, 2H), 3.85 (t, 2H), 7.05 (d, 1H), 7.1-7.35 (m, 3H).

MS (APCI) : M/Z (MH^+) 318.6; $C_{21}H_{35}NO$ + H requires 318.3.

Example 35: 1-Hexyl-3,4-dimethyl-4-(3-(1-hydroxy-2-methylamino)-ethylphenyl)piperidine

To a solution of 1-hexanoyl-3,4-dimethyl-4-{3-[4-(4-methylphenyl)-sulfonyl-4,5-dihydro-1,3-oxazol-5-yl]phenyl}piperidine (Preparation 10, 345 mg, 0.68 mmol) in anhydrous tetrahydrofuran (5 mL) at room temperature was added lithium aluminium hydride (1.0 M solution in tetrahydrofuran, 0.74 mL, 0.74 mmol) dropwise over five minutes. The solution was stirred at room temperature under a nitrogen atmosphere for 2 hours and then cooled to 0°C. The reaction was quenched cautiously by the addition of aqueous sodium hydroxide solution (1.0 mL, 1.0 *N*) and then ethyl acetate (20 mL) and solid sodium hydrogencarbonate (excess)

were added. The mixture was stirred vigorously for 30 minutes and then filtered through Celite®, washing with ethyl acetate. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel eluted with neat ethyl acetate and then ethyl acetate : methanol : 0.880 ammonia (70:30:1) to give the title compound as a clear gum (120 mg).

NMR ($CDCl_3$, selected data) : 0.75 (d, 3H), 0.9 (t, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (m, 1H), 2.0 (m, 1H), 2.2-2.6 (m, 9H), 2.65-2.85 (m, 3H), 4.75 (m, 1H), 7.1-7.35 (m, 4H).

MS (thermospray) : M/Z (MH^+) 347.3; $C_{22}H_{38}N_2O$ + H requires 347.3.

Preparation of Starting Materials

Preparation 1: 1-Hexyl-3,4-dimethyl-4-(3-trifluoromethanesulfonyloxy-phenyl)piperidine

To a solution of 1-hexyl-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (3.5 g, 12 mmol, *J. Med. Chem.*, 1993, **36**, 2833) in dichloromethane (15 mL) was added triethylamine (3 mL) followed by *N*-phenyltrifluoromethanesulfonimide (6.1 g, 18 mmol) portionwise. The reaction mixture was stirred under nitrogen at room temperature for 18 hours then it was washed with aqueous sodium hydroxide solution (60 mL of 2 *N*). The separated aqueous layer was back-washed with dichloromethane (2 x 30 mL), after which the combined organics were dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow oil. This was purified by column chromatography on silica gel (150 g) eluted with hexane : ethyl acetate : 0.880 ammonia (66:33:1) to give the title compound as a yellow oil (4.22 g).

NMR ($CDCl_3$) : 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.7 (m, 3H), 2.0 (m, 1H), 2.2-2.45 (m, 4H), 2.45-2.65 (m, 2H), 2.8 (m, 1H), 7.1 (d, 1H), 7.15 (s, 1H), 7.25-7.45 (m, 2H).

MS (thermospray) : M/Z (MH^+) 422.3; $C_{20}H_{30}F_3NO_3S$ + H requires 422.2.

Preparation 2: 1-Benzyl-3,4-dimethyl-4-(3-trifluoromethanesulfonyl-oxyphenyl)piperidine

To a stirred solution of 1-benzyl-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine (10.16 g, 34.4 mmol, *J. Med. Chem.*, 1993, **36**, 2833) in anhydrous dichloromethane (100 mL) was added triethylamine (8 mL) and the resulting solution was de-oxygenated by evacuating and flushing with nitrogen three times. *N*-Phenyltrifluoromethanesulfonimide (18.43 g, 51.6 mmol) was added and the mixture was de-oxygenated again, using the same procedure as before, and stirred overnight at room temperature under nitrogen. The reaction mixture was then diluted with dichloromethane (200 mL) and washed with aqueous sodium hydroxide solution (200 mL of 1 *N*). The aqueous phase was back-washed with dichloromethane (2 x 100 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give an orange oil (*ca* 20 g) which was purified by column chromatography on silica gel (700 g) eluted with a gradient of ethyl acetate : hexane : 0.880 ammonia (10:190:1 to 10:90:1). This gave the title compound as a colourless oil (13.98 g).

NMR ($CDCl_3$) : 0.75 (d, 3H), 1.35 (s, 3H), 1.55 (m, 1H), 1.95 (m, 1H), 2.25-2.5 (m, 2H), 2.5-2.65 (m, 2H), 2.85 (m, 1H), 3.45 (d, 1H), 3.6 (d, 1H), 7.1 (d, 1H), 7.15 (s, 1H), 7.2-7.45 (m, 7H).

MS (thermospray) : M/Z (MH^+) 428.0; $C_{21}H_{24}F_3NO_3S$ + H requires 428.2.

Preparation 3: 3,4-Dimethyl-4-(3-(*N*-ethyl)amidophenyl)piperidine

To a solution of 1-benzyl-3,4-dimethyl-4-(3-(*N*-ethyl)amidophenyl)-piperidine (Example 16, 800 mg, 2.3 mmol) in methanol (40 mL) was added palladium on activated carbon (150 mg, Degussa type E101 NE/W, Pd 10% dry weight, *ca* 50% water). The resulting suspension was stirred at room temperature under an atmosphere of hydrogen at 415 kPa for 1½ days. It was then filtered through Celite® to remove the catalyst residues and concentrated *in vacuo* to give a foam (610 mg). Purification by column chromatography on silica gel (30 g) eluted with CH_2Cl_2 : EtOH : 0.880 ammonia (50:8:1) gave the title compound as a thick gum (557 mg).

NMR ($CDCl_3$, selected data) : 0.7 (d, 3H),1.25 (t, 3H), 1.4 (s, 3H), 1.95 (m, 1H), 2.15 (m, 1H), 2.75 (m, 1H), 2.95-3.15 (m, 2H), 3.25 (m, 1H), 3.5 (m, 2H), 7.3-7.45 (m, 2H), 7.5 (d, 1H), 7.7 (s, 1H).

MS (APCI) : M/Z (MH^+) 261.5; $C_{16}H_{24}N_2O$ + H requires 261.2.

Preparation 4: 1-Hexyl-3,4-dimethyl-4-{3-[2-(trimethylsilyl)ethynyl]-phenyl}piperidine

To a solution of 1-hexyl-3,4-dimethyl-4-(3-trifluoromethanesulfonyloxy-phenyl)piperidine (Preparation 1, 350 mg, 0.83 mmol) in tetrahydrofuran (12 mL) was added diisopropylamine (4 mL) and trimethylsilylethyne (4.5 g, 46 mmol) and the mixture was de-oxygenated by evacuating and flushing with nitrogen five times. Copper(I) iodide (6.2 mg 0.033 mmol), and then catalytic quantities of palladium(II) acetate and 1,1'-bis(diphenyl-phosphino)ferrocene were added. The reaction mixture was heated to reflux under nitrogen for 8 hours, before being allowed to cool to room temperature. Water (10 mL) and dichloromethane (10 mL) were added, the phases separated and the aqueous layer further extracted with dichloromethane (2 x 10 mL). The combined organics were then dried

(Na_2SO_4) and the solvent removed *in vacuo*. The residual brown oil was purified by column chromatography on silica gel (25 g) eluted with a gradient of ethyl acetate : hexane : 0.880 ammonia (20:79:1 to 50:49:1) to give the title compound as an oil (150 mg).

NMR ($CDCl_3$) : 0.25 (s, 9H), 0.75 (d, 3H), 0.9 (m, 3H), 1.2-1.4 (m, 9H), 1.4-1.55 (m, 2H), 1.6 (m, 1H), 2.0 (m, 1H), 2.2-2.4 (m, 4H), 2.4-2.6 (m, 2H), 2.8 (m, 1H), 7.2-7.35 (m, 3H), 7.4 (s, 1H).

MS (thermospray) : M/Z (MH^+) 370.4; $C_{24}H_{39}NSi$ + H requires 370.3.

Preparation 5: 1-Hexanoyl-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine

To a stirred solution of 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (3.8 g, 18.6 mmol, *J. Org. Chem.*, 1991, **56**, 1660) in dichloromethane (30 mL) at 0°C was added triethylamine (3.9 mL, 27.8 mmol) followed by the dropwise addition of hexanoic anhydride (4.7 mL, 20.4 mmol) over 5 minutes. The reaction was stirred under a nitrogen atmosphere for 3 hours at room temperature and then quenched by the addition of saturated aqueous sodium hydrogencarbonate (50 mL). The two layers were separated and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with ethyl acetate : hexane (1:1). The title compound was obtained as a clear oil (4.5 g).

NMR ($CDCl_3$, selected data from a 13:9 mixture of rotamers) : 0.65 (d, 3H), 0.9 (m, 3H), 1.25-1.45 (m, 7H), 1.55-1.75 (m, 3H), 2.05 (m, 1H), 2.15 (m, 1H), 2.25-2.55 (m, 2H), 2.95 (m, 0.59H), 3.15 (m, 0.41H), 3.35 (m, 0.41H), 3.5-3.7 (m, 1.18H), 3.85 (m, 0.41H), 4.4 (m, 0.41H), 4.75 (m, 0.59H), 6.7 (d, 1H), 6.75-6.85 (m, 2H), 7.15 (t, 1H).

MS (thermospray) : M/Z (MH^+) 304.1; $C_{19}H_{29}NO_2$ + H requires 304.2.

Preparation 6: 1-Hexanoyl-3,4-dimethyl-4-(trifluoromethanesulfonyl-oxyphenyl)piperidine

To a stirred solution of 1-hexanoyl-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine (Preparation 5, 3.1 g, 10.1 mmol) in dichloromethane (30 mL) at room temperature was added triethylamine (2.82 mL, 20.2 mmol) followed by *N*-phenyltrifluoromethanesulfonimide (3.6 g, 15.1 mmol) portionwise. The reaction was stirred under a nitrogen atmosphere at room temperature for 16 hours and then aqueous sodium hydroxide (30 mL of 2 *N*) was added. The bi-phasic mixture was stirred vigorously for 2 hours before the two layers were separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with a gradient of ethyl acetate : hexane (1:2 and then 2:1). The title compound was obtained as a clear oil (3.6 g).

NMR ($CDCl_3$, selected data from a 7:5 mixture of rotamers) : 0.55-0.65 (m, 3H), 0.85-0.95 (m, 3H), 1.25-1.4 (m, 4H), 1.45 (s, 3H), 1.55-1.75 (m, 3H), 2.0-2.5 (m, 4H), 2.9 (m, 0.58H), 3.15 (m, 0.42H), 3.35 (m, 0.42H), 3.6 (m, 1.16H), 3.9 (m, 0.42H), 4.4 (m, 0.42H), 4.75 (m, 0.58H), 7.05-7.15 (m, 2H), 7.3 (m, 1H), 7.4 (m, 1H).

MS (thermospray) : M/Z (MH^+) 436.4; $C_{20}H_{28}F_3NO_4S$ + H requires 436.2.

Preparation 7: 1-Hexanoyl-3,4-dimethyl-4-(3-methoxycarbonylphenyl)-piperidine

To a solution of 1-hexanoyl-3,4-dimethyl-4-(trifluoromethanesulfonyloxyphenyl)piperidine (Preparation 6, 267 mg, 0.48 mmol) in anhydrous *N,N*-dimethylformamide (2 mL) was added triethylamine (0.18 mL) and methanol (0.4 mL). The mixture was de-oxygenated by evacuating and flushing with nitrogen five times. Palladium(II) acetate (4.4 mg) and 1,1'-bis(diphenylphosphino)ferrocene (8 mg) were added and the solution was purged with carbon monoxide. The reaction mixture was heated to 60°C under an atmosphere of carbon monoxide for 7 hours then it was cooled to room temperature and diluted with saturated aqueous sodium chloride solution (10 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (4 x 15 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (50 g) eluted with hexane : ethyl acetate : 0.880 ammonia (66:33:1). The title compound was obtained as a pale yellow oil (110 mg).

NMR ($CDCl_3$, selected data from a 9:7 mixture of rotamers) : 0.55-0.7 (m, 3H), 0.85-0.95 (m, 3H), 1.25-1.4 (m, 4H), 1.45 (s, 3H), 1.6-1.8 (m, 3H), 2.05-2.45 (m, 4H), 2.9 (m, 0.56H), 3.15 (m, 0.44H), 3.4 (m, 0.44H), 3.6 (m, 1.12H), 3.9 (m, 0.44H), 3.95 (s, 3H), 4.4 (0.44H), 4.7 (m, 0.56H), 7.35-7.5 (m, 2H), 7.9 (m, 1H), 7.95 (m, 1H).

MS (thermospray) : M/Z (MH^+) 346.3; $C_{21}H_{31}NO_3$ + H requires 346.2.

Preparation 8: 1-Hexanoyl-3,4-dimethyl-4-(3-vinylphenyl)piperidine

To a stirred solution of 1-hexanoyl-3,4-dimethyl-4-(trifluoromethanesulfonyloxyphenyl)piperidine (Preparation 6, 3.0 g, 6.90 mmol) in tetrahydrofuran (30 mL) at room temperature were added sequentially

vinyltributyltin (2.12 mL, 7.24 mmol), lithium chloride (585 mg, 13.8 mmol), and tetrakis(triphenylphosphine)palladium(0) (80 mg, 0.69 mmol). The mixture was heated to reflux under a nitrogen atmosphere for 1½ hours at which time a few crystals of 4-*tert*-butylcatechol were added. Heating at reflux was then continued for a further 16 hours. The mixture was cooled and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with a gradient of ethyl acetate : hexane (1:10 to 1:3). The title compound was obtained as a clear oil (2.1 g).

NMR ($CDCl_3$, selected data from a 5:4 mixture of rotamers) : 0.55-0.7 (m, 3H), 0.85-1.0 (m, 3H), 1.25-1.4 (m, 4H), 1.4 (s, 3H), 1.6-1.75 (m, 3H), 2.05-2.45 (m, 4H), 2.9 (m, 0.56H), 3.15 (m, 0.44H), 3.35 (m, 0.44H), 3.6 (m, 1.12H), 3.9 (m, 0.44H), 4.4 (m, 0.44H), 4.7 (m, 0.56H), 5.25 (d, 1H), 5.75 (d, 1H), 6.7 (dd, 1H), 7.15 (m, 1H), 7.2-7.35 (m, 3H).

MS (APCI) : M/Z (MH^+) 314.5; $C_{21}H_{31}NO$ + H requires 314.2.

Preparation 9: 1-Hexanoyl-3,4-dimethyl-4-(3-formylphenyl)piperidine

To a solution of 1-hexanoyl-3,4-dimethyl-4-(3-vinylphenyl)piperidine (Preparation 8, 2.4 g, 7.67 mmol) in acetone (20 mL) at room temperature was added water (5 mL), 4-methylmorpholine *N*-oxide (1.1 g, 9.20 mmol) and finally osmium tetroxide (3.83 mL, 2.5 wt % solution in *tert*-butanol). The yellow solution was stirred at room temperature for 1 hour and then sodium periodate (4.92 g, 23.0 mmol) was added in one portion. After stirring the reaction for 3 hours a heavy precipitate had developed and the reaction mixture was filtered through Celite®, washing with acetone. The filtrate was concentrated *in vacuo*, the crude oil was dissolved in dichloromethane, dried ($MgSO_4$) and concentrated *in vacuo*. The residue

was purified by column chromatography on silica gel eluting with ethyl acetate : hexane (1:1). The title compound was isolated as clear oil (2.0 g).

NMR ($CDCl_3$, selected data from a 1:1 mixture of rotamers) : 0.55-0.7 (m, 3H), 0.85-0.95 (m, 3H), 1.25-1.4 (m, 4H), 1.45 (s, 3H), 1.55-1.8 (m, 3H), 2.1-2.5 (m, 4H), 2.95 (m, 0.5H), 3.15 (m, 0.5H), 3.4 (m, 0.5H), 3.6 (m, 1H), 3.9 (m, 0.5H), 4.4 (m, 0.5H), 4.75 (m, 0.5H), 7.45-7.6 (m, 2H), 7.7 (m, 1H), 7.75 (m, 1H), 10.0 (s, 1H).

MS (thermospray) : M/Z (MH^+) 316.3; $C_{20}H_{29}NO_2$ + H requires 316.2.

Preparation 10: 1-Hexanoyl-3,4-dimethyl-4-{3-[4-(4-methylphenyl)-sulfonyl-4,5-dihydro-1,3-oxazol-5-yl]phenyl}piperidine

To a solution of 1-hexanoyl-3,4-dimethyl-4-(3-formylphenyl)piperidine (Preparation 9, 758 mg, 2.40 mmol) in ethanol (20 mL) was added [(4-methylphenyl)sulfonyl]methyl isocyanide (460 mg, 2.34 mmol) followed by sodium cyanide (12 mg, 0.24 mmol). The mixture was stirred at room temperature under a nitrogen atmosphere for five hours and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using a gradient elution of hexane : ethyl acetate (67:33 to 0:100). The title compound was isolated as a clear oil (909 mg).

NMR ($CDCl_3$) (selected data from a 1:1 mixture of rotamers) : 0.55-0.65 (m, 3H), 0.85-0.95 (m, 3H), 1.25-1.45 (m, 7H), 1.55-1.75 (m, 3H), 2.05-2.45 (m, 4H), 2.45 (s, 3H), 2.9 (m, 0.5H), 3.15 (m, 0.5H), 3.35 (m, 0.5H), 3.6 (m, 1H), 3.9 (m, 0.5H), 4.4 (m, 0.5H), 4.7 (m, 0.5H), 5.0 (d, 1H), 6.05 (d, 1H), 7.1-7.3 (m, 4H), 7.3-7.45 (m, 3H), 7.85 (d, 2H).

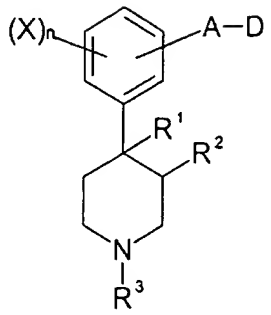
MS (thermospray) : M/Z (MH^+) 511.1; $C_{29}H_{38}N_2O_4S$ + H requires 511.3.

Biological Activity

The Ki values of certain compounds of the present invention in the opioid receptor binding assays were determined, and the compounds of Examples 4, 8, 18 and 20 were all found to have Ki values of 4000 nM or less for the μ receptor. The compounds of the invention also possess affinity at the δ and κ opioid receptors.

Claims

1. A compound of formula I,



I

wherein A represents a single bond, C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH;

D represents H, OH, CN, $N(R^4)(R^5)$, $N(H)R^6$, $C(O)N(R^4)(R^5)$, $C(O)OR^7$, $C(O)R^8$, $C(=NR^{9a})R^8$, or $C(=NOR^{9b})R^8$;

provided that when A represents C_{2-4} alkenylene or C_{2-4} alkynylene, and D represents OH, $N(R^4)(R^5)$ or $N(H)R^6$, then D is not directly attached to an unsaturated carbon atom;

and provided that when A represents a single bond, then D does not represent H, OH, $N(R^4)(R^5)$ or $N(H)R^6$;

R^4 and R^5 independently represent H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, C_{1-4} alkylphenyl, which latter four groups are optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), or R^4 and R^5, together with the N-atom to which they are attached, form a 4- to 7-membered heterocyclic ring, which ring

optionally contains one or more additional heteroatoms selected from oxygen, nitrogen and sulfur and which ring is optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, OH, =O, nitro, amino or halo;

R^6 represents $C(O)R^{10a}$, $C(O)OR^{10b}$ or $S(O)_2R^{10c}$;

R^{10a} to R^{10c} independently represent C_{1-4} alkyl, C_{3-8} cycloalkyl, aryl, C_{1-4} alkylphenyl (which four groups are all optionally substituted by or one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms)), or R^{10a} represents H;

R^7 and R^8 independently represent H, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl or C_{1-4} alkylphenyl, which latter four groups are optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms);

R^{9a} and R^{9b} independently represent C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, C_{1-4} alkylphenyl, which latter four groups are optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), or R^{9b} represents H;

R^1 and R^2 are each independently H or C_{1-4} alkyl;

R^3 represents aryl (optionally substituted by one or more substituents selected from OH, nitro, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms) and $-N(R^{11a})(R^{11b})$), C_{1-10} alkyl, C_{3-10} alkenyl or C_{3-10} alkynyl wherein said alkyl, alkenyl or alkynyl groups

are optionally substituted and/or terminated by one or more substituents selected from OR^{11c}, $S(O)_pR^{11d}$, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^{12a})S(O)_2R^{13}$, Het^1, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or $-W-A^1-N(R^{12b})(R^{12c})$;

p is 0, 1 or 2;

W represents a single bond, C(O) or $S(O)_q$;

A^1 represents a single bond or C_{1-10} alkylene;

provided that when both W and A^1 represent single bonds, then the group $-N(R^{12b})(R^{12c})$ is not directly attached to an unsaturated carbon atom;

q is 0, 1 or 2;

R^{11a} to R^{11d} each independently represent H, C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl, aryl (which latter six groups are optionally substituted by or one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)) or Het^2;

provided that R^{11d} does not represent H when p represents 1 or 2;

R^{12a} to R^{12c} each independently represent H, C_{1-10} alkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl, aryl (which latter six groups are optionally substituted by or one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), Het^3, or R^{12b} and R^{12c} together represent unbranched C_{2-6} alkylene which alkylene group is optionally

interrupted by O, S and/or an N(R^{14}) group and is optionally substituted by one or more C_{1-4} alkyl groups;

R^{13} represents C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-4} alkylphenyl or aryl, which four groups are optionally substituted by or one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, OH, nitro, amino or halo;

R^{14} represents H, C_{1-6} alkyl, C_{3-8} cycloalkyl, A^2-(C_{3-8} cycloalkyl) or A^2-aryl;

A^2 represents C_{1-6} alkylene;

Het^1, Het^2 and Het^3 independently represent 3- to 8-membered heterocyclic groups, which groups contain at least one heteroatom selected from oxygen, sulfur and/or nitrogen, which groups are optionally fused to a benzene ring, and which groups are optionally substituted in the heterocyclic and/or fused benzene ring part by one or more substituents selected from OH, =O, nitro, amino, halo, CN, aryl, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms);

X is H, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms);

n is 0, 1 or 2;

or pharmaceutically, or veterinarily, acceptable derivatives thereof.

2. A compound as claimed in Claim 1 wherein the group A-D is attached in the *meta*- position relative to the piperidine ring.

3. A compound as claimed in Claim 1 or Claim 2 wherein R^1 represents C_{1-2} alkyl.

4. A compound as claimed in any one of Claims 1 to 3 wherein R^2 represents H or C_{1-2} alkyl.

5. A compound as claimed in any one of Claims 1 to 4 wherein R^3 represents saturated C_{1-10} alkyl, optionally substituted by one or more substituents selected from OR^{11c}, CN, halo, C_{2-4} alkanoyl, C_{1-4} alkoxy carbonyl, $N(R^{12a})SO_2R^{13}$, Het^1, aryl (which latter group is optionally substituted by one or more substituents selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-5} alkanoyl, halo, nitro, amino, CN and $CONH_2$), or $-W-A^1-N(R^{12b})(R^{12c})$.

6. A compound as claimed in any one of Claims 1 to 5 wherein R^{11c} represents H, C_{1-6} alkyl or aryl (which latter groups is optionally substituted by one or more substituents selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-5} alkanoyl, halo, nitro, amino, CN and $CONH_2$); R^{12a} to R^{12c} independently represent H, C_{1-4} alkyl, C_{1-2} alkylphenyl or aryl (which latter three groups are optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl or C_{1-4} alkoxy); W represents C(O); and/or A^1 represents a single bond.

7. A compound as claimed in any one of Claims 1 to 6 wherein R^{13} represents C_{1-4} alkyl, C_{1-2} alkylphenyl or aryl (which three groups are all optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl or C_{1-4} alkoxy).

8. A compound as claimed in any one of Claims 1 to 7 wherein A represents a single bond, C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene,

which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more OH and/or methyl groups.

9. A compound as claimed in any one of Claims 1 to 8 wherein D represents H, OH, CN, $N(H)R^4$, $N(H)C(O)R^{10a}$, $N(H)C(O)OR^{10b}$, $N(H)S(O)_2R^{10c}$, $C(O)N(R^4)(R^5)$, $C(O)OR^7$, $C(O)R^8$ or $C(=NOH)R^8$; R^4 and R^5 independently represent H, C_{1-4} alkyl or C_{1-3} alkylphenyl, which latter two groups are optionally substituted by C_{1-4} alkoxy; R^7 and R^8 independently represent H or C_{1-4} alkyl; and/or R^{10a} to R^{10c} independently represent C_{1-4} alkyl, which group is optionally substituted by one or more halo atoms.

10. A compound as claimed in any one of Claims 1 to 9 wherein R^3 represents saturated C_{1-7} alkyl, optionally substituted by one or more substituents selected from CN, O-(C_{1-6} alkyl), phenyl, or O-(phenyl).

11. A compound as claimed in any one of Claims 1 to 10 wherein X represents halo.

12. A compound as claimed in any one of Claims 1 to 11 wherein n represents 0 or 1.

13. A compound as defined in any one of Claims 1 to 12, for use as a medicament.

14. A compound as defined in any one of Claims 1 to 12, for use as an animal medicament.

15. A formulation comprising a compound as defined in any one of Claims 1 to 12, in admixture with a pharmaceutically, or a veterinarily, acceptable adjuvant, diluent or carrier.

16. A formulation as claimed in Claim 15, which is a veterinary formulation.

17. The use of a compound as defined in any one of Claims 1 to 12, in the manufacture of a medicament for the curative or prophylactic treatment of a disease mediated *via* an opiate receptor.

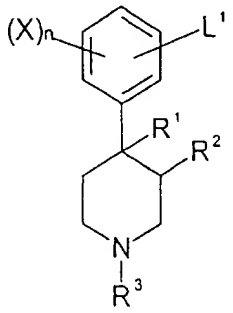
18. The use as claimed in Claim 17, wherein the disease is pruritus.

19. A method of treating or preventing a disease mediated by an opiate receptor, which comprises administering a therapeutically effective amount of a compound as defined in any one of Claims 1 to 12, to a patient in need of such treatment.

20. A process for the preparation of a compound as defined in Claim 1, which comprises:

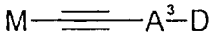
a) for compounds of formula I in which A represents C_{2-4} alkynylene (in which group the carbon-carbon triple bond is α,β to the benzene ring), which alkynylene group is optionally substituted at the 3- and/or the 4-C (relative to the benzene ring) by one or more substituents defined in Claim 1 in respect of A, and/or one of the groups defined in Claim 1 in respect of D, or (when D is not attached at the 3- or 4-C) which alkynylene group is substituted at the 2-C (relative to the benzene ring) by CN,

$C(O)N(R^4)(R^5)$, $C(O)OR^7$, $C(O)R^8$, $C(=NR^{9a})R^8$, or $C(=NOR^{9b})R^8$, reaction of a corresponding compound of formula II,



II

wherein L^1 is a leaving group, and R^1, R^2, R^3, X and n are as defined in Claim 1, with a compound of formula III,

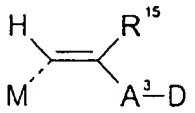


III

wherein M represents (as appropriate) H, a tin-containing moiety, a boron derivative, a zinc halide, a magnesium halide or an alkali metal, A^3 represents a single bond or C_{1-2} alkylene (optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, OH or halo), and D is as defined in Claim 1, provided that when A^3 represents a single bond, then D does not represent H, OH, $N(R^4)(R^5)$ or $N(H)R^6$, wherein R^4, R^5 and R^6 are as defined in Claim 1;

b) for compounds of formula I in which A represents C_{2-4} alkenylene (in which group the carbon-carbon double bond is α,β to the benzene ring), which alkenylene group is optionally substituted at the 2-C (relative to the benzene ring) by C_{1-4} alkyl, and also optionally substituted at the 3- and/or 4-C (relative to the benzene ring) by one or more of the substituents defined in Claim 1 in respect of A and/or one of the groups defined in Claim 1 in respect of D, or which alkenylene group is substituted at the 2-C (relative to the benzene ring) by CN, $C(O)N(R^4)(R^5)$, $C(O)OR^7$, $C(O)R^8$, $C(=NR^{9a})R^8$, or $C(=NOR^{9b})R^8$, reaction of a corresponding

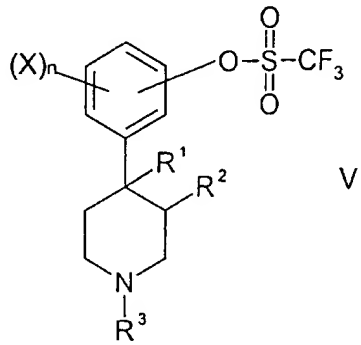
compound of formula II, as defined above, with a compound of formula IV,



IV

wherein the dashed bond represent optional *cis*- or *trans*- geometry, R^{15} represents H or C_{1-4} alkyl, A^3 and M are as defined above, and D is as defined in Claim 1;

c) for compounds of formula I in which A represents a single bond and D represents CN, reaction of a compound of formula V,



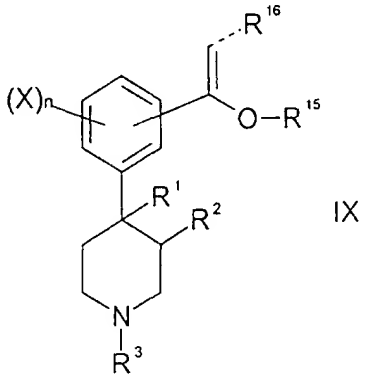
V

wherein R^1, R^2, R^3, X and n are as defined in Claim 1, with an alkali metal cyanide ;

d) for compounds of formula I in which A represents C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents NH_2 (which is attached to a CH_2 group), reduction of a corresponding compound of formula I in which A represents (as appropriate) a single bond, C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents CN;

e) for compounds of formula I in which D represents $C(O)NH_2$, controlled hydrolysis of a corresponding compound of formula I in which D represents CN;

f) for compounds of formula I in which A represents a single bond and D represents C(O)-(C_{1-6} alkyl) or C(O)-(C_{1-4} alkylphenyl), which alkyl and alkylphenyl groups are both optionally substituted by one or more of the substituents defined in Claim 1 in respect of R^8, hydrolysis of a corresponding compound of formula IX,



IX

wherein R^{15} represents C_{1-6} alkyl, R^{16} represents H, C_{1-5} alkyl, phenyl or C_{1-3} alkylphenyl which latter three groups are all optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), the dashed bond indicates optional *cis*- or *trans*- geometry, and R^1, R^2, R^3, X and n are as defined in Claim 1;

g) for compounds of formula I in which D represents $C(O)R^8$, wherein R^8 is as defined in Claim 1 provided that it does not represent H, reaction of a corresponding compound of formula I in which D represents CN with an organometallic compound capable of delivering an R^{8a}-containing anion, wherein R^{8a} is defined as for R^8 in Claim 1 provided that it does not represent H;

h) for compounds of formula I in which A represents a single bond and D represents $C(O)OR^7$, wherein R^7 is as defined in Claim 1 provided that it does not represent H, reaction of a corresponding compound of formula V, as defined above, with carbon monoxide and an alcohol of formula $R^{7a}OH$, wherein R^{7a} is defined as for R^7 in Claim 1 provided that it does not represent H;

i) for compounds of formula I in which A represents C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents OH (which is attached to a CH_2 group), reduction of a corresponding compound of formula I in which A represents (as appropriate) a single bond, C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents $C(O)OR^{7a}$, wherein R^{7a} is as defined above;

j) for compounds of formula I in which A represents C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are *gem*-disubstituted with two C_{1-4} alkyl groups (α to D) and are optionally substituted by one or more further substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents OH, reaction of a corresponding compound of formula I in which A represents (as appropriate) a single bond, C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents $C(O)OR^{7a}$, wherein R^{7a} is as defined above, with a C_{1-4} alkyl-delivering organometallic compound;

k) for compounds of formula I in which D represents $C(O)N(R^4)(R^5)$, wherein R^4 and R^5 are as defined in Claim 1:

A) reaction of a corresponding compound of formula I in which D represents $C(O)OR^{7a}$, wherein R^{7a} is as defined above, with a compound of formula XI,

$HN(R^4)(R^5)$ XI

or an acid addition salt thereof, wherein R^4 and R^5 are as defined in Claim 1;

B) reaction of a corresponding compound of formula I in which D represents C(O)OH with a compound of formula XI, as defined above.

l) for compounds of formula I in which D represents C(O)OH, hydrolysis of a corresponding compound of formula I in which D represents $C(O)OR^{7a}$, wherein R^{7a} is as defined above;

m) for compounds of formula I in which D represents $N(H)R^6$, wherein R^6 is as defined in Claim 1, reaction of a corresponding compound of formula I in which D represents NH_2 with a compound of formula XII,

R^6-L^1 XII

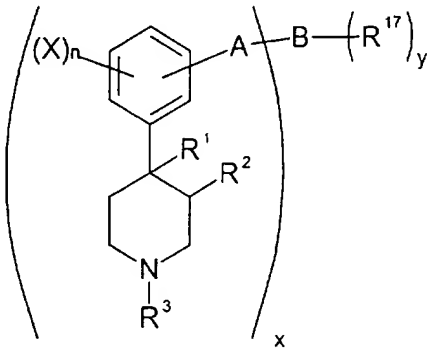
wherein R^6 is as defined in Claim 1 and L^1 is as defined above;

n) for compounds of formula I in which A represents C_{1-4} alkyl and D represents $N(R^4)(R^5)$ or $N(H)C(O)R^{10a}$ attached at the 1-, 2- or 3-C (relative to the benzene ring), wherein R^4, R^5 and R^{10a} are as defined in Claim 1, reaction of a corresponding compound of formula I in which A represents C_{1-4} alkenylene unsaturated α,β-, β,γ- or γ,δ- (respectively) relative to the benzene ring and D represents H, with a compound of formula XI, as defined above, or a compound of formula XIII,

NC-R^{10a} XIII

wherein R^{10a} is as defined in Claim 1;

o) for compounds of formula I in which A represents C_{2-4} alkylene optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents OH, oxidation of a corresponding borane adduct of formula XIV,



XIV

wherein x is 1, 2 or 3, y is (as appropriate) (3-x) or 1, R^{17} is (as appropriate) H, halo, an alkyl, or a cycloalkyl group providing one or two bonds to boron, A represents (as appropriate) C_{2-4} alkylene optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and R^1, R^2, R^3, X and n are as defined in Claim 1;

p) for compounds of formula I in which A represents a C_{2-4} alkylene group substituted (α to D) with an OH group and D represents OH, reaction of a corresponding compound of formula I in which A represents a C_{2-4} alkenylene group and D represents H with a dihydroxylating reagent;

q) for compounds of formula I in which A represents a single bond or a C_{1-2} alkylene group (as appropriate) and D represents C(O)H, reaction of a corresponding of formula I in which A represents a C_{2-4} alkylene group substituted (α to D) with an OH group and D represents OH with a reagent that effects 1,2-diol oxidative cleavage;

r) for compounds of formula I in which D represents $C(=NR^{9a})R^8$ or $C(=NOR^{9b})R^8$, wherein R^8, R^{9a} and R^{9b} are as defined in Claim 1,

reaction of a corresponding compound of formula I in which D represents $C(O)R^8$ with a compound of formula XV,

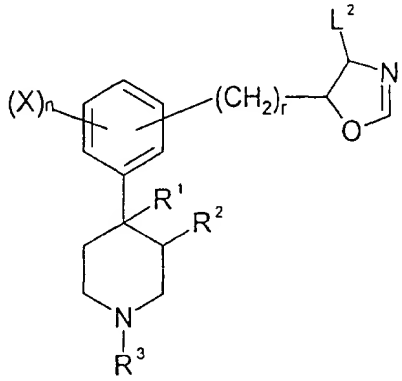
$$H_2N\text{-}R^{9a} \qquad XV$$

or a compound of formula XVI,

$$H_2N\text{-}OR^{9b} \qquad XVI$$

wherein R^{9a} and R^{9b} are as defined in Claim 1;

s) for compounds of formula I in which A represents C_{1-4} alkylene substituted (α to D) with an OH group and D represents $N(H)CH_3$ (at the alkylene chain terminus), reduction of a corresponding compound of formula XVII,

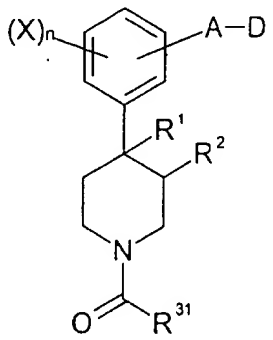


XVII

wherein r is 0, 1 or 2, L^2 represents H or a group capable, when attached to a C_2 alkylene unit, of undergoing 1,2-elimination (relative to L^2), and R^1, R^2, R^3, X and n are as defined in Claim 1;

t) for compounds of formula I wherein R^3 represents C_1 alkyl optionally substituted by C_{3-8} cycloalkyl, Het^1, aryl, adamantyl, (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or R^3 represents C_{2-10} alkyl, C_{3-10} alkenyl or C_{3-10} alkynyl (which three groups are all optionally substituted by one or more of the relevant substituents identified in Claim 1 in respect to R^3),

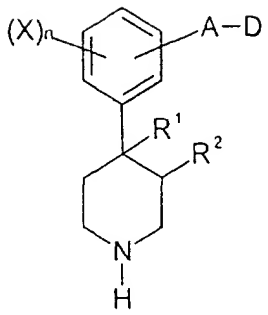
which alkyl, alkenyl or alkynyl groups are attached to the piperidine nitrogen atom *via* a CH_2 group, wherein Het^1 is as defined in Claim 1, reduction of a corresponding compound of formula XIX,



XIX

wherein R^{31} represents H, C_{3-8} cycloalkyl, Het^1, aryl, adamantyl, (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), C_{1-9} alkyl, C_{2-9} alkenyl or C_{2-9} alkynyl, which alkyl, alkenyl or alkynyl groups are optionally substituted and/or terminated by one or more substituents selected from OR^{11c}, $S(O)_pR^{11d}$, CN, halo, C_{1-6} alkoxy carbonyl, C_{2-6} alkanoyl, C_{2-6} alkanoyloxy, C_{3-8} cycloalkyl, C_{4-9} cycloalkanoyl, $N(R^{12a})S(O)_2R^{13}$, Het^1, aryl, adamantyl (which latter two groups are optionally substituted by one or more substituents selected from OH, nitro, amino, halo, CN, CH_2CN, $CONH_2$, C_{1-4} alkyl, C_{1-4} alkoxy and C_{1-5} alkanoyl (which latter three groups are optionally substituted by one or more halo atoms)), or $-W-A^1-N(R^{12b})(R^{12c})$, and R^1, R^2, R^{11c}, R^{11d}, R^{12a} to R^{12c}, R^{13}, Het^1, n, p, W, X, A^1, A and D are as defined in Claim 1;

u) reaction of a corresponding compound of formula XX,



XX

wherein R^1, R^2, A, D, X and n are as defined in Claim 1, with a compound of formula VIII,

R^3-L^1 VIII

wherein R^3 is as defined in Claim 1 and L^1 is as defined above;

v) for compounds of formula I wherein R^3 represents C_1 alkyl, which, in place of being optionally substituted by the substituents as defined in Claim 1, is instead optionally substituted by R^{31}, wherein R^{31} is as defined above, reaction of a corresponding compound of formula XX, as defined above, with a compound of formula XXII,

$R^{31}CHO$ XXII

wherein R^{31} is as defined above, in the presence of a reducing agent;

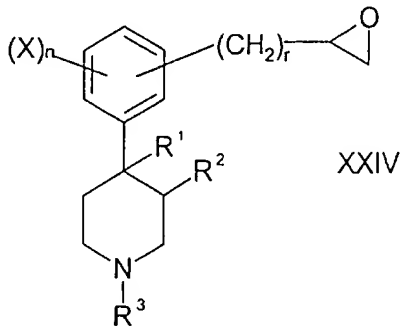
w) for compounds of formula I wherein R^3 is a C_{1-10} alkyl, C_{4-10} alkenyl or C_{4-10} alkynyl group that is fully saturated from 1- to 3-C (relative to the piperidine N-atom), and which R^3 group is substituted at 2-C (relative to the piperidine N-atom) by $S(O)R^{11d}$, $S(O)_2R^{11d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, $-C(O)-A^1-N(R^{12b})(R^{12c})$, $-S(O)-A^1-N(R^{12b})(R^{12c})$, or $-S(O)_2-A^1-N(R^{12b})(R^{12c})$, wherein R^{11d}, R^{12b}, R^{12c} and A^1 are as defined in Claim 1, reaction of a corresponding compound of formula XX, as defined above, with a compound of formula XXIII,

R^{3a}-Z XXIII

wherein R^{3a} represents R^3 as defined in Claim 1 except that it does not represent aryl, and that the R^{3a} chain contains an additional carbon-carbon

double bond α,β to the Z-substituent, and Z represents $S(O)R^{11d}$, $S(O)_2R^{11d}$, alkanoyl, cycloalkanoyl, alkoxy carbonyl, CN, $-C(O)-A^1-N(R^{12b})(R^{12c})$, $-S(O)-A^1-N(R^{12b})(R^{12c})$, or $-S(O)_2-A^1-N(R^{12b})(R^{12c})$, wherein R^{11d}, R^{12b}, R^{12c} and A^1 are as defined in Claim 1;

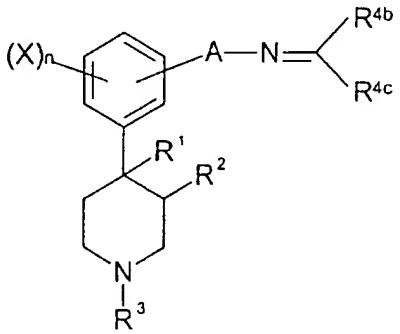
x) for compounds of formula I in which A represents C_{2-4} alkylene substituted (α to D) with an OH group and D represents $N(R^4)(R^5)$ (at the alkylene chain terminus), and R^4 and R^5 are as defined in Claim 1, reaction of a compound of formula XXIV,



XXIV

wherein R^1, R^2, R^3, X and n are as defined in Claim 1 and r is as defined above, with a compound of formula XI, as defined above;

y) for compounds of formula I in which D represents $N(H)R^4$, wherein R^4 is as defined in Claim 1 provided that it does not represent aryl, reduction of a corresponding compound of formula XXV,



XXV

wherein R^{4b} and R^{4c}, together with the carbonyl group to which they are attached, form a C_{1-6} alkanal, C_{3-6} alkanone, C_{3-8} cycloalkanone, phenyl(C_{1-4})alkanal or phenyl(C_{2-4})alkanone group, which five groups are

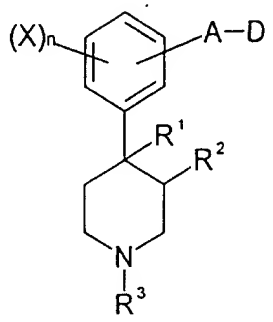
optionally substituted by one or more substituents selected from nitro, halo, C_{1-4} alkyl or C_{1-4} alkoxy (which latter two groups are optionally substituted by one or more halo atoms), and R^1, R^2, R^3, A, X and n are as defined in Claim 1 (provided that the $-N=C(R^{4b})(R^{4c})$ group is not directly attached to an unsaturated carbon atom);

z) for compounds of formula I in which A represents C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents $N(R^4)(R^5)$ (attached to a CH_2 group), wherein R^4 and R^5 are as defined in Claim 1, reduction of a corresponding compound of formula I in which A represents (as appropriate) a single bond, C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene, which alkylene, alkenylene or alkynylene groups are optionally substituted by one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, halo or OH, and D represents $C(O)N(R^4)(R^5)$;

aa) conversion of one functional group on an alkyl, heterocyclic or aryl group in a compound of formula I to another.

ABSTRACT

There is provided a compound of formula I,



I

wherein A, D, R^1, R^2, R^3, X and n have meanings given in the description, which are useful in the prophylaxis and in the treatment of diseases mediated by opiate receptors, such as pruritus.


THE PATENT OFFICE
18 MAY 2000
LONDON

Antrag auf Erteilung eines europäischen Patents / Request for grant of a European patent / Requête en délivrance d'un brevet européen

1

Bestatigung einer bereits durch Telefax eingereichten Anmeldung / Confirmation of an application already filed by facsimile / Confirmation d'une demande déjà déposée par téléfax
Wenn ja, Datum der Übermittlung des Telefax und Name der Einreichungsbehörde / If yes, facsimile date and name of the authority with which the documents were filed / Si oui, date d'envoi du télefax et nom de l'autorité de dépôt

☐ Ja / Yes / Oui

Datum / Date | Behörde / Authority / Autorité

C. DE ALMEIDA

Nur fur amtlichen Gebrauch / For official use only / Cadre réservé à l'administration

Anmeldenummer / Application No / N° de la demande	MKEY	1	00304219.9
Tag des Eingangs (Regel 24(2)) / Date of receipt (Rule 24(2)) / Date de réception (règle 24(2))	DREC	2	18 MAY 2000
Tag des Eingangs beim EPA (Regel 24(4)) / Date of receipt at EPO (Rule 24(4)) / Date de réception à l'OEB (règle 24(4))	RENA	3	EPO DG 1 30. 05. 2000
Anmeldetag / Date of filing / Date de dépôt		4	

Tabulatoren-Positionen / Tabulation marks / Arrêts de tabulation

Es wird die Erteilung eines europäischen Patents und gemäß Artikel 94 die Prüfung der Anmeldung beantragt / Grant of a European patent, and examination of the application under Article 94, are hereby requested / Il est demandé la délivrance d'un brevet européen et, conformément à l'article 94, l'examen de la demande — EXAM 4 — 5

☒ *Prüfungsantrag in einer zugelassenen Nichtamtssprache (siehe Merkblatt II, 5) / Request for examination in an admissible non-EPO language (see Notes II,5) / Requête en examen dans une langue non officielle autorisée (voir notice II,5)*

Zeichen des Anmelders oder Vertreters (max 15 Positionen) / Applicant's or representative's reference (maximum 15 spaces) / Référence du demandeur ou du mandataire (max 15 caractères ou espaces) — AREF — 6: SE/9484/82936

Anmelder / Applicant / Demandeur

Name / Nom — 7: PFIZER INC.,

Anschrift / Address / Adresse — 8:
235 East 42nd Street,
New York,
New York 10017-5755,
United States of America
(for all countries except Great Britain)

APPR 01 # 012010916219
DEST

Zustellanschrift / Address for correspondence / Adresse pour la correspondance — 9:
URQUHART-DYKES & LORD,
30 Welbeck Street,
London, W1M 7PG,
Great Britain

PADR

Staat des Wohnsitzes oder Sitzes / State of residence or of principal place of business / Etat du domicile ou du siège — 10: New York, New York, U.S.A.

Staatsangehörigkeit / Nationality / Nationalité — 11: a corporation organised under the laws ~~of the State of Delaware, U.S.A.~~

Telefon / Telephone / Téléphone — 12:

Telex / Télex | Telefax / Fax / Téléfax — 13:

Weitere(r) Anmelder auf Zusatzblatt / Additional applicant(s) on additional sheet / Autre(s) demandeur(s) sur feuille additionnelle — 14: ☐

Vertreter / Representative / Mandataire

Name / Nom — 15: EDDOWES, Simon

(**Nur einen** Vertreter angeben, der in das europäische Patentregister eingetragen ist und an den zugestellt wird / Name **only one** representative who is to be listed in the Register of European Patents and to whom notification is to be made / N'indiquer qu'**un seul** mandataire, qui sera inscrit au Registre européen des brevets et auquel signification sera faite)

FREP 01 087418216 # #1 #

Geschäftsanschrift / Address of place of business / Adresse professionnelle — 16:
URQUHART-DYKES & LORD
30 Welbeck Street,
London, W1M 7PG,
Great Britain

Telefon / Telephone / Téléphone — 17: 44 (0) 20 7487 1550

Telex / Télex | Telefax / Fax / Téléfax — 18: 44 (0) 20 7487 1598

Weitere(r) Vertreter auf Zusatzblatt / Additional representative(s) on additional sheet / Autre(s) mandataire(s) sur feuille additionnelle — 19: X

TRAN | FILL EN

SE/9484/82936
Raum für Zeichen des Anmelders / Space for applicant's reference / Espace réservé à la référence du demandeur

Vollmacht / Authorisation / Pouvoir

ist beigefugt / is enclosed / joint

ist registriert unter Nummer / has been registered under No / a été enregistré sous le n° GENA

20 ☐

21 Nummer / Number / Numéro

Erfinder / Inventor / Inventeur INVT 20 # #

Anmelder ist (sind) alleinige(r) Erfinder / The applicant(s) is (are) the sole inventor(s) / Le(s) demandeur(s) est (sont) le (les) seul(s) inventeur(s)

22 ☐

Erfindernennung in gesondertem Schriftstuck / Designation of inventor attached / Voir la désignation de l'inventeur ci-jointe

23 ☒

Bezeichnung der Erfindung / Title of invention / Titre de l'invention

TIDE TIEN TIFR

24 NEW 4-ARYLPIPERIDINE DERIVATIVES FOR THE TREATMENT OF PRURITUS

Prioritätserklärung / Declaration of priority / Déclaration de priorité PRIO

25

	Staat / State / Etat	Anmeldetag / Date of filing / Date de dépôt	Aktenzeichen / Application No / N° de la demande
01 # # # EN#	1 Great Britain	28 May 1999	99 12 411.7
02 # # #	2		
03 # # #	3		
04 # # #	4		

Weitere Prioritatserklarung(en) auf Zusatzblatt / Additional declaration(s) of priority on additional sheet / Autre(s) déclaration(s) de priorité sur feuille additionnelle ☐

Es wird hiermit erklärt, daß die Anmeldung eine vollständige Übersetzung der früheren Anmeldung ist (Regel 38(4) / It is hereby declared that the application is a complete translation of the previous application (Rule 38(4) / Il est déclaré par la présente que la demande est une traduction intégrale de la demande antérieure (règle 38(4) PRIO 6

25a ☐

Biologisches Material

Die Erfindung bezieht sich auf bzw verwendet biologisches Material, das nach Regel 28 hinterlegt worden ist

Biological material

The invention relates to and/or uses biological material deposited under Rule 28

26 ☐

Matière biologique

L'invention concerne et/ou utilise de la matière biologique, déposée conformément à la règle 28

Die Angaben nach Regel 28(1)c) (falls noch nicht bekannt, die Hinterlegungsstelle und das (die) Bezugszeichen [Nummer, Symbole usw] des Hinterlegers) sind in den technischen Anmeldungsunterlagen enthalten auf / The particulars referred to in Rule 28(1)(c) (if not yet known, the depository institution and the identification reference(s) [number, symbols etc] of the depositor) are given in the technical documents in the application on / Les indications visées à la règle 28(1)c) (si pas encore connues, l'autorité de dépôt et la (les) référence(s) d'identification [numéro ou symboles etc] du déposant) figurent dans les pièces techniques de la demande à la /aux

BIOM 1 # | | | | | | #

27

Seite(n) / page(s)	Zeile(n) / line(s) / ligne(s)

werden spater mitgeteilt / will be submitted later /seront communiquées ultérieurement 27a ☐

Die Empfangsbescheinigung(en) der Hinterlegungsstelle ist (sind) beigefugt / The receipt(s) of deposit issued by the depositary institution is (are) enclosed / Le(s) récépissé(s) de dépôt délivré(s) par l'autorité de dépôt est (sont) joint(s) 27b ☐

wird (werden) nachgereicht / will be filed later /sera (seront) produit(s) ultérieurement 27c ☐

SE/9484/82936

Raum fur Zeichen des Anmelders / Space for applicant's reference / Espace réservé à la référence du demandeur

Falls das biologische Material nicht vom Anmelder, sondern von einem Dritten hinterlegt wurde / Where the biological material has been deposited by a person other than the applicant / Lorsque la matière biologique a été déposée par une personne autre que le demandeur

Ermächtigung nach Regel 28(1)d) / Authorisation under Rule 28(1)(d) / L'autorisation en vertu de la règle 28(1)d)

ist beigefugt / is enclosed / est jointe

wird nachgereicht / will be filed later / sera produite ultérieurement

28 Name und Anschrift des Hinterlegers / Name and address of depositor / Nom et adresse du déposant

28a ☐

28b ☐

Verzicht auf die Verpflichtung des Antragstellers nach Regel 28(3) in gesondertem Schriftstück / Waiver of the right to an undertaking from the requester pursuant to Rule 28(3) attached

29 ☐ Renonciation, sur document distinct, à l'engagement du requérant au titre de la règle 28(3)

Gemäß Regel 28(4) wird hiermit mitgeteilt, daß der Zugang zu dem in den Feldern 26 und 27 genannten biologischen Material nur durch Herausgabe einer Probe an einen Sachverstandigen hergestellt wird / It is hereby declared under Rule 28(4) that the availability of the biological material referred to in Sections 26 and 27 shall be effected only by the issue of a sample to an expert

BIOM 3

30 ☐ Conformément à la règle 28(4) il est déclaré par la présente que l'accessibilité à la matière biologique mentionée aux rubriques 26 et 27 ne peut réalisée que par la remise d'un échantillon à un expert

Nucleotid- und Aminosäuresequenzen / Nucleotide and amino acid sequences / Séquences de nucléotides et d'acides aminés

SEQL 1

31

Die Beschreibung enthalt ein Sequenzprotokoll nach Regel 27a(1) / The description contains a sequence listing in accordance with Rule 27a(1) / La description contient une liste de séquences selon la règle 27bis(1)

Der vorgeschriebene Datenträger ist beigefugt / The prescribed data carrier is enclosed / Le support de données prescrit est joint

Es wird hiermit erklart, daß die auf dem Datentrager gespeicherte Information mit dem schriftlichen Sequenzprotokoll übereinstimmt (Regel 27a(2)) / It is hereby stated that the information recorded on the data carrier is identical to the written sequence listing (Rule 27a(2)) / Il est déclaré par la présente que l'information figurant sur le support de données est identique à celle que contient la liste de séquences écrite (règle 27bis(2))

Benennung der Vertragsstaaten und Erklärungen hierzu

Designation of contracting states and associated declarations

DEST

32

Désignation d'Etats contractants et déclarations à ce propos

1 Hiermit werden samtliche Vertragsstaaten des EPU benannt, die diesem bei Einreichung dieser Anmeldung angehören*

Mit der Zahlung des **siebenfachen** Betrags einer Benennungsgebühr gelten die Benennungsgebühren fur alle Vertragsstaaten als entrichtet (Art 2 Nr 3 GebO)

1 All states which are contracting states to the EPC at the filing of this application are hereby designated*

Payment of **seven times** the amount of the designation fee is deemed to constitute payment of the designation fees for all the contracting states (Art 2, No 3, RFees)

☒ 1 Sont désignés tous les Etats qui sont des Etats contractants de la CBE à la date du dépôt de la présente demande*

Les taxes de désignation sont réputées acquittées pour tous les Etats contractants dès lors qu'un montant correspondant à **sept fois** la taxe de désignation a été acquitté (art 2, point 3 du RRT)

2 Es ist derzeit beabsichtigt, **weniger als sieben** Benennungsgebühren für folgende Vertragsstaaten zu entrichten *(bitte Landercodes und Vertragsstaaten angeben*)*

2 It is currently intended to pay **fewer than seven** designation fees for the following contracting states *(please indicate country codes and contracting states*)*

☐ 2 Il est actuellement envisagé de payer **moins de sept** taxes de désignation pour les Etats contractants suivants *(prière d'indiquer codes de pays et Etats contractants*)*

(1) ☐ _____

(2) ☐ _____

(3) ☐ _____

(4) ☐ _____

(5) ☐ _____

(6) ☐ _____

Es wird beantragt, fur die unter Nr 2 nicht aufgefuhrten Vertragsstaaten von der Zustellung von Mitteilungen nach Regel 85a(1) und Regel 69(1) abzusehen

No communications under Rules 85a(1) or 69(1) need be notified in respect of the contracting states not indicated under No 2

Prière de ne pas procéder à la signification des notifications prévues par les règles 85bis(1) et 69(1) pour les Etats contractants n'ayant pas été mentionnés au n° 2

3 Wird ein **automatischer Abbuchungsauftrag** erteilt (Feld 43), so wird das EPA beauftragt, bei Ablauf der Grundfrist nach Artikel 79(2) den siebenfachen Betrag einer Benennungsgebühr abzubuchen Ist eine Erklarung unter Nr 2 abgegeben worden, so sollen die Benennungsgebühren nur fur die dort angegebenen Vertragsstaaten abgebucht werden, sofern dem EPA nicht bis zum Ablauf der Grundfrist ein anderslautender Auftrag zugeht

3 If an **automatic debit order** has been issued (Section 43), the EPO is authorised, on expiry of the basic period under Article 79(2), to debit seven times the amount of the designation fee If any states are indicated under No 2, the EPO shall debit designation fees only for those states, unless it is instructed to do otherwise before expiry of the basic period

☒ 3 Si un **ordre de prélèvement automatique** est donné (rubrique 43), il est demandé à l'OEB de prélever, à l'expiration du délai normal visé à l'article 79(2), un montant correspondant à sept fois la taxe de désignation Si une déclaration a été faite au n° 2, les taxes de désignation ne sont prélevées que pour les Etats contractants qui y sont indiqués, sauf instruction contraire reçue par l'OEB avant l'expiration du délai normal

* Stand bei Drucklegung 19 Vertragsstaaten, und zwar / Status when this form was printed 19 contracting states, namely / Situation à la date d'impression 19 Etats contractants, à savoir **AT** Osterreich / Austria / Autriche, **BE** Belgien / Belgium / Belgique, **CH/LI** Schweiz und Liechtenstein / Switzerland and Liechtenstein / Suisse et Liechtenstein, **CY** Zypern / Cyprus / Chypre, **DE** Deutschland / Germany / Allemagne, **DK** Danemark / Denmark / Danemark, **ES** Spanien / Spain / Espagne, **FI** Finnland / Finland / Finlande, **FR** Frankreich / France / France, **GB** Vereinigtes Konigreich / United Kingdom / Royaume-Uni, **GR** Griechenland / Greece / Grèce, **IE** Irland / Ireland / Irlande, **IT** Italien / Italy / Italie, **LU** Luxemburg / Luxembourg / Luxembourg, **MC** Monaco / Monaco / Monaco, **NL** Niederlande / Netherlands / Pays-Bas, **PT** Portugal / Portugal / Portugal, **SE** Schweden / Sweden / Suède

SE/9484/82936

Raum fur Zeichen des Anmelders / Space for applicant's reference / Espace réservé à la référence du demandeur

Verschiedene Anmelder fur verschiedene Vertragsstaaten /
Different applicants for different contracting states /
Différents demandeurs pour différents Etats contractants

APPR 02 # 02093107#

33 Name(n) des (der) Anmelder(s) und benannte Vertragsstaaten /
Name(s) of applicant(s) and designated contracting states /
Nom(s) du (des) demandeur(s) et des Etats contractants désignés

PFIZER LIMITED,
Ramsgate Road,
Sandwich,
Kent, CT13 9NJ,
Great Britain.
(for Great Britain only)

Erstreckung des europäischen Patents

Diese Anmeldung gilt als Antrag, die europaische Patentanmeldung und das darauf erteilte europaische Patent auf alle Nicht-Vertragsstaaten des EPU zu erstrecken, mit denen am Tag ihrer Einreichung „Erstreckungsabkommen" bestehen (derzeit Albanien, Litauen, Lettland, Rumanien, Slowenien, ehemalige jugoslawische Republik Mazedonien) Die Erstreckung wird jedoch nur wirksam, wenn die vorgeschriebene Erstreckungsgebühr entrichtet wird

Extension of the European patent

This application is deemed to be a request to extend the European patent application and the European patent granted in respect of it to all non-contracting states to the EPC with which "extension agreements" exist on the date on which the application is filed (Present situation Albania, Lithuania, Latvia, Romania, Slovenia, former Yugoslav Republic of Macedonia) However, the extension only takes effect if the prescribed extension fee is paid

EXPT

34 **Extension des effets du brevet européen**

☒ La présente demande est réputée constituer une requête en extension des effets de la demande de brevet européen et du brevet européen délivré sur la base de cette demande à tous les Etats non parties à la CBE avec lesquels il existe un «accord d'extension» à la date du dépôt de la demande (Situation actuelle . Albanie, Lituanie, Lettonie, Roumanie, Slovénie, ex-République yougoslave de Macédoine) Toutefois, l'extension ne produit ses effets que s'il est acquitté la taxe d'extension prescrite

Es ist derzeit beabsichtigt, die Erstreckungsgebühr fur die nachfolgend angekreuzten Staaten zu entrichten / It is currently intended to pay the extension fee for the states marked below with a cross / Il est actuellement envisagé de payer la taxe d'extension pour les Etats dont le nom est coché ci-après

Albanien / Albania / Albanie	AL ☐
Litauen / Lithuania / Lituanie	LT ☐
Lettland / Latvia / Lettonie	LV ☐
Rumanien / Romania / Roumanie	RO ☐
Slowenien / Slovenia / Slovénie	SI ☐
Ehemalige jugoslawische Republik Mazedonien / Former Yugoslav Republic of Macedonia / Ex-République yougoslave de Macédoine	MK ☐
_____	☐
_____	☐

(Platz fur Staaten, mit denen nach Drucklegung dieses Formblatts „Erstreckungsabkommen" in Kraft treten) / (Space for states with which "extension agreements" enter into force after this form has been printed) / (Prévu pour des Etats à l'égard desquels des «accords d'extension» entreront en vigueur après l'impression du présent formulaire)

Die Anmeldung ist eine Teilanmeldung /
The application is a divisional application /
La présente demande constitue une demande divisionnaire

DFIL 9 # PANR #

35 ☐ Nummer der früheren Anmeldung
No of earlier application
Numéro de la demande initiale

Es handelt sich um eine Anmeldung nach Artikel 61(1)b) /
The application is an Article 61(1)(b) application /
La présente demande constitue une demande selon l'article 61(1)b)

DFIL 9 # EANR #

36 ☐ Nummer der fruheren Anmeldung
No of earlier application
Numéro de la demande initiale

Patentansprüche / Claims / Revendications CLMS

37 20 Zahl der Patentansprüche
Number of claims
Nombre de revendications

Zur Veroffentlichung mit der Zusammenfassung wird vorgeschlagen Abbildung Nr /
It is proposed that the abstract be published together with figure No /
Il est proposé de publier avec l'abrégé la figure n°

DRAW 2

39 ☐ Nummer / Number / Numéro

SE/9484/82936
Raum fur Zeichen des Anmelders / Space for applicant's reference / Espace réservé à la référence du demandeur

Zusätzliche Abschrift(en) der im europäischen Recherchenbericht angeführten Schriftstücke wird (werden) beantragt /
Additional copy(ies) of the documents cited in the European search report is (are) requested /
Prière de fournir une (des) copie(s) supplémentaire(s) des documents cités dans le rapport de recherche européenne

ASOC

40 | 1 | Anzahl der **zusätzlichen** Sätze von Abschriften / Number of **additional** sets of copies / Nombre de jeux **supplémentaires** de copies

Es wird die Rückerstattung der Recherchengebühr gemäß Art 10 GebO beantragt / Refund of the search fee is requested pursuant to Article 10 of the Rules relating to Fees / Le remboursement de la taxe de recherche est demandé en vertu de l'article 10 du règlement relatif aux taxes

41 ☐

Eine Kopie des Recherchenberichts ist beigefügt /
A copy of the search report is attached /
Une copie du rapport de recherche est jointe

42 ☐

Automatischer Abbuchungsauftrag
(nur möglich für Inhaber von beim EPA geführten laufenden Konten)

Das EPA wird hiermit beauftragt, fällig werdende Gebühren und Auslagen nach Maßgabe der Vorschriften über das automatische Abbuchungsverfahren vom nebenstehenden laufenden Konto abzubuchen. In bezug auf die **Benennungsgebühren** wird auf Feld 32.3 verwiesen. Das EPA wird ferner beauftragt, die **Erstreckungsgebühren** für jeden in Feld 34 angekreuzten »Erstreckungsstaat« bei Ablauf der Grundfrist zu ihrer Zahlung abzubuchen, sofern ihm nicht bis dahin ein anderslautender Auftrag zugeht

Automatic debit order
(for EPO deposit account holders only)

The EPO is hereby authorised, under the Arrangements for the automatic debiting procedure, to debit from the deposit account opposite any fees and costs falling due. With regard to **designation fees** reference is made to Section 32.3. The EPO is also authorised, on expiry of the basic period for its payment, to debit the **extension fee** for each of the "extension states" marked with a cross in Section 34, unless it is instructed to do otherwise before expiry of this period

43

Ordre de prélèvement automatique
(possibilité offerte uniquement aux titulaires de comptes courants ouverts auprès de l'OEB)

Par la présente, il est demandé à l'OEB de prélever du compte courant ci-dessous les taxes et frais venant à échéance, conformément à la réglementation relative à la procédure de prélèvement automatique. Pour les **taxes de désignation,** se reporter à la rubrique 32.3. Il est en outre demandé à l'OEB de prélever, à l'expiration du délai normal prévu pour leur paiement, les **taxes d'extension** pour chaque «Etat autorisant l'extension» coché à la rubrique 34, sauf instruction contraire reçue avant l'expiration de ce délai

Für automatischen Abbuchungsauftrag:
For automatic debit order:
Pour l'ordre de prélèvement automatique :

DECA

Nummer des laufenden Kontos / Deposit account number / Numéro du compte courant

Name des Kontoinhabers / Account holder's name / Nom du titulaire du compte

Eventuelle **Rückzahlungen** auf das nebenstehende beim EPA geführte laufende Konto / **Reimbursement,** if any, to EPO deposit account opposite / **Remboursements** éventuels à effectuer sur le compte courant ci-contre ouvert auprès de l'OEB

DEPA

Nummer des laufenden Kontos / Deposit account number / Numéro du compte courant

Name des Kontoinhabers / Account holder's name / Nom du titulaire du compte

44 | 2805.0046

Die vorgeschriebene Liste über die diesem Antrag beigefügten Unterlagen ergibt sich aus der vorbereiteten Empfangsbescheinigung (Seite 6 dieses Antrages)

The prescribed list of documents enclosed with this request is shown on the prepared receipt (page 6 of this request)

45 | La liste prescrite des documents joints à cette requête figure sur le récépissé préétabli (page 6 de la présente requête)

Unterschrift(en) des (der) Anmelder(s) oder Vertreter(s) /
Signature(s) of applicant(s) or representative(s) /
Signature(s) du (des) demandeur(s) ou du (des) mandataire(s)

46 | Für Angestellte nach Artikel 133(3) Satz 1 mit allgemeiner Vollmacht / For employees under Article 133(3), 1st sentence, having a general authorisation / Pour les employés mentionnés à l'article 133(3), 1ère phrase, munis d'un pouvoir général

Nr / No / n°

Ort / Place / Lieu London, Great Britain.

Datum / Date 08 May 2000

Simon Eddowes

Simon EDDOWES
URQUHART-DYKES & LORD

Name des (der) Unterzeichneten bitte in Druckschrift wiederholen. Bei juristischen Personen bitte die Stellung des (der) Unterzeichneten innerhalb der Gesellschaft in Druckschrift angeben / Please print name under signature. In the case of legal persons, the position of the signatory within the company should also be printed / Le ou les noms des signataires doivent être indiqués en caractères d'imprimerie. S'il s'agit d'une personne morale, la position occupée au sein de celle-ci par le ou les signataires doit être indiquée en caractères d'imprimerie

Raum für Zeichen des Anmelders / Space for applicant's reference / Espace réservé à la référence du demandeur

Empfangsbescheinigung / Receipt for documents / Récépissé de documents 6

(Liste der diesem Antrag beigefugten Unterlagen) (Checklist of enclosed documents) (Liste des documents annexés à la présente requête)

Es wird hiermit der Empfang der unten bezeichneten Dokumente bescheinigt / Receipt of the documents indicated below is hereby acknowledged / Nous attestons le dépôt des documents désignés ci-dessous

Wird im Falle der Einreichung der europaischen Patentanmeldung bei einer nationalen Behorde diese Empfangsbescheinigung vom Europaischen Patentamt ubersandt, so ist sie als Mitteilung gemaß Regel 24(4) anzusehen (siehe Feld RENA) **Nach Erhalt der Mitteilung nach Regel 24(4) sind alle weiteren Unterlagen, die die Anmeldung betreffen, nur noch unmittelbar beim EPA einzureichen.** / If this receipt is issued by the European Patent Office and the European patent application was filed with a national authority it serves as a communication under Rule 24(4) (see Section RENA) **Once the communication under Rule 24(4) has been received, all further documents relating to the application must be sent directly to the European Patent Office.** / Si, en cas de dépôt de la demande de brevet européen auprès d'un service national, l'Office européen des brevets délivre le présent récépissé de documents, ce récépissé est reputé être la notification visée à la règle 24(4) (cf rubrique RENA) **Dès que la notification visée à la règle 24(4) a été reçue, tous les autres documents relatifs à la demande doivent être adressés directement à l'OEB.**

Simon Eddowes,
URQUHART-DYKES & LORD,
30 Welbeck Street,
London, W1M 7PG,
Great Britain.

Nur fur amtlichen Gebrauch / For official use only / Cadre réservé à l'administration

Datum / Date

THE PATENT OFFICE
18 MAY 2000
LONDON

Unterschrift / An *ichet officiel*

Anmeldenummer / Application No / N° de la demande			00304219.9
Tag des Eingangs (Regel 24(2)) / Date of receipt (Rule 24(2)) / Date de réception (règle 24(2))	DREC		18 MAY 2000
Zeichen des Anmelders/Vertreters / Applicant's/ Representative's ref / Référence du demandeur ou du mandataire	AREF		SE/9484/82936

Nur nach Einreichung der Anmeldung bei einer nationalen Behorde / Only after filing of the application with a national authority / Seulement après le dépôt de la demande auprès d'un service national

Tag des Eingangs beim EPA (Regel 24(4)) / Date of receipt at EPO (Rule 24(4)) / Date de réception à l'OEB (règle 24(4))	RENA		

			Stückzahl / Number of copies / Nombre d'exemplaires	Blattzahl* eines Stucks / Number of sheets* in each copy / Nombre de feuilles* par exemplaire	Gesamtzahl der Abbildungen* / Total number of figures* / Nombre total de figures*
A.	**Anmeldungsunterlagen und Prioritätsbeleg(e) / Application documents and priority document(s) / Pièces de la demande et document(s) de priorité**	47			
1	Beschreibung (ohne Sequenzprotokollteil) / Description (excluding sequence listing part) / Description (sauf partie reservée au listage des séquences)		3	74	
2	Patentanspruche / Claim(s) / Revendication(s)		3	18	
3	Zeichnung(en) / Drawing(s) / Dessin(s) DRAW 1 #		-	-	
4	Sequenzprotokollteil der Beschreibung / Sequence listing part of description / Partie de la description réservée au listage des séquences				
5	Zusammenfassung / Abstract / Abrégé		3	1	
6	Ubersetzung der Anmeldungsunterlagen / Translation of the application documents / Traduction des pièces de la demande				
7	Prioritatsbeleg(e) / Priority document(s) / Document(s) de priorité		enclosed		
8	Ubersetzung des (der) Prioritatsbelegs(belege) / Translation of priority document(s) / Traduction du (des) document(s) de priorité				

B	**Der Anmeldung in der eingereichten Fassung liegen folgende Unterlagen bei: / This application as filed is accompanied by the items below: / A la présente demande sont annexées les pièces suivantes:**	48	
1	Einzelvollmacht / Specific authorisation / Pouvoir particulier		
2	Allgemeine Vollmacht / General authorisation / Pouvoir général		
3	Erfindernennung / Designation of inventor / Désignation de l'inventeur		X
4	Fruherer Recherchenbericht / Earlier search report / Rapport de recherche antérieure		
5	Gebuhrenzahlungsvordruck (EPA Form 1010) / Voucher for the settlement of fees (EPO Form 1010) / Bordereau de règlement de taxes (OEB Form 1010)		X
6	Scheck *(nicht bei Einreichung bei den nationalen Behorden)* / Cheque *(not when filing with national authorities)* / Chèque *(pas de chèque en cas de dépôt auprès des services nationaux)*		
7	Datentrager fur Sequenzprotokoll / Data carrier for sequence listing / Support de données pour liste de séquences SEQL 4		
8	Zusatzblatt / Additional sheet / Feuille additionnelle		X
9	Sonstige Unterlagen (bitte hier spezifizieren) / Other documents (please specify here) / Autres documents (veuillez préciser)		

Wahrung Betrag / Currency Amount / Monnaie Montant
(Ausfullung freigestellt / optional / facultatif)

C.	**Kopien dieser Empfangsbescheinigung / Copies of this receipt for documents / Copies du présent récépissé de documents**	49	3 Anzahl der Kopien / Number of copies / Nombre de copies

* Die Richtigkeit der Angabe der Blattzahl und der Gesamtzahl der Abbildungen wurde bei Eingang nicht geprüft / No check was made on receipt that the number of sheets and the total number of figures indicated were correct / L'exactitude du nombre de feuilles et du nombre total de figures n'a pas ete controlee lors du dépôt

SE/9484/82936
Raum fur Zeichen des Anmelders / Space for applicant's reference / Espace reservé à la référence du demandeur

ADDITIONAL SHEET

ADDITIONAL REPRESENTATIVES

BEN-NATHAN, Laurence Albert
GREEN, Mark Charles
SIMPSON, Alison Elizabeth Fraser
REES, Alexander Ellison

PLACE OF BUSINESS

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Erfindernennung
Designation of inventor
Désignation de l'inventeur

(falls Anmelder nicht oder nicht allein der Erfinder ist) / (where the applicant is not the inventor or is not the sole inventor) / (si le demandeur n'est pas l'inventeur ou l'unique inventeur)

Nr. der Anmeldung oder, falls noch nicht bekannt, Bezeichnung der Erfindung.
Application No or, if not yet known, title of the invention:
N° de la demande ou, s'il n'est pas encore connu, titre de l'invention :

NEW 4-ARYLPIPERIDINE DERIVATIVES FOR THE TREATMENT OF PRURITUS

Zeichen des Anmelders oder Vertreters
Applicant's or representative's reference
Référence du demandeur ou du mandataire
(max 15 Positionen / max 15 spaces / 15 caractères au maximum)

SE/9484/82936

In Sachen der obenbezeichneten europäischen Patentanmeldung nennt (nennen) der (die) Unterzeichnete(n)[1]
In respect of the above European patent application I (we), the undersigned[1]
En ce qui concerne la demande de brevet européen susmentionnée, le(s) soussigné(s)[1]

PFIZER INC.,
235 East 42nd Street,
New York,
New York 10017-5755,
United States of America.

(for all countries except Great Britain)

PFIZER LIMITED,
Ramsgate Road,
Sandwich,
Kent, CT13 9NJ.
Great Britain.

(for Great Britain only)

als Erfinder[2].
do hereby designate as inventor(s)[2].
désigne(nt) en tant qu'inventeur(s)[2].

ARMER, Richard Edward,
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Research and Development,
Organon Laboratories Limited,
Newhouse,
Scotland, ML1 5SH,
Great Britain

GETHIN, David Morris,
Pfizer Central Research,
Ramsgate Road,
Sandwich,
Kent, CT13 9NJ,
Great Britain

[X] Weitere Erfinder sind auf einem gesonderten Blatt angegeben. / Additional inventors indicated on supplementary sheet / D'autres inventeurs sont mentionnés sur une feuille supplémentaire

Der (Die) Anmelder hat (haben) das Recht auf das europäische Patent erlangt[3]
The applicant(s) has (have) acquired the right to the European patent[3]
Le(s) demandeur(s) a (ont) acquis le droit au brevet européen[3]

[X] gemäß Vertrag vom / under an agreement dated / par contrat en date du 10 May 1999

[X] als Arbeitgeber / as employer(s) / en qualité d'employeur(s)

[ ] durch Erbfolge / as successor(s) in title / par transfert successoral

Ort/Place/Lieu London, Great Britain

Datum/Date 08 May 2000

Unterschrift(en) des (der) Anmelder(s) oder Vertreter(s)
Signature(s) of applicant(s) or representative(s)
Signature(s) du (des) demandeur(s) ou du (des) mandataire(s) :

Simon Eddowes

Simon EDDOWES - URQUHART-DYKES & LORD

Name des (der) Unterzeichneten bitte mit Schreibmaschine wiederholen. Bei juristischen Personen bitte die Stellung des (der) Unterzeichneten innerhalb der Gesellschaft mit Schreibmaschine angeben / Please type name under signature. In the case of legal persons, the position of the signatory within the company should also be typed / Le ou les noms des signataires doivent être également dactylographiés. S'il s'agit d'une personne morale, la position occupée au sein de celle-ci par le ou les signataires sera indiquée à la machine à écrire

Fußnoten siehe Rückseite. / Footnotes overleaf. / Le texte des renvois figure au verso.

bitte wenden / P.T.O. / T.S.V.P.

DESIGNATION OF INVENTOR

als Erfinder
do hereby designate as inventor(s)
designe(nt) en tant qu'inventeur(s)

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